VOLUME 79 June 1958 NUMBER 6

THE JOURNAL OF
UROLOGY

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Annual Meeting, American Urological Association, Chalfonte Haddon Hall
Atlantic City N J, April 20-23, 1959

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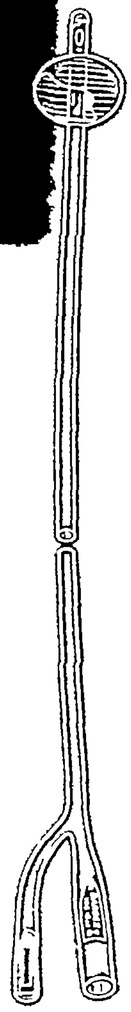

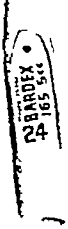

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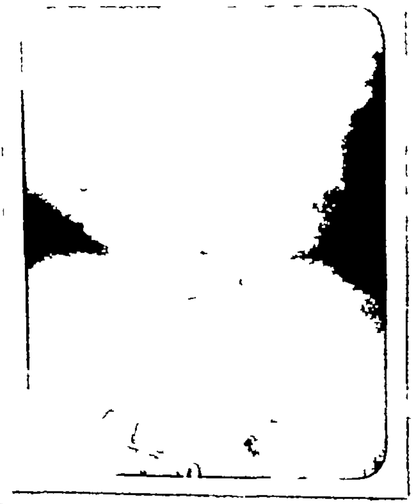
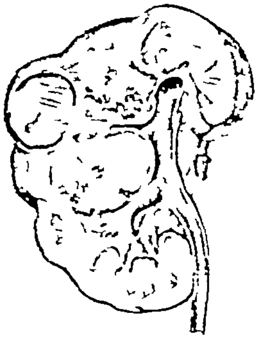


Retrograde pyelogram with Skiodan showing compression of right renal pelvis.



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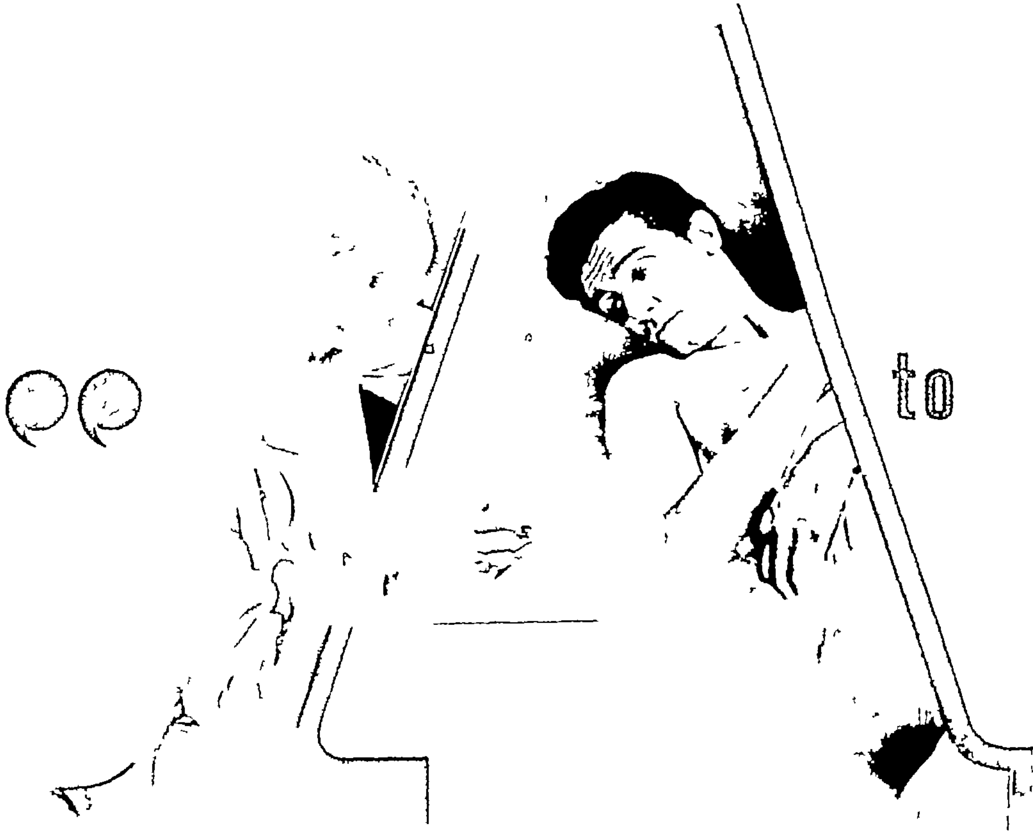

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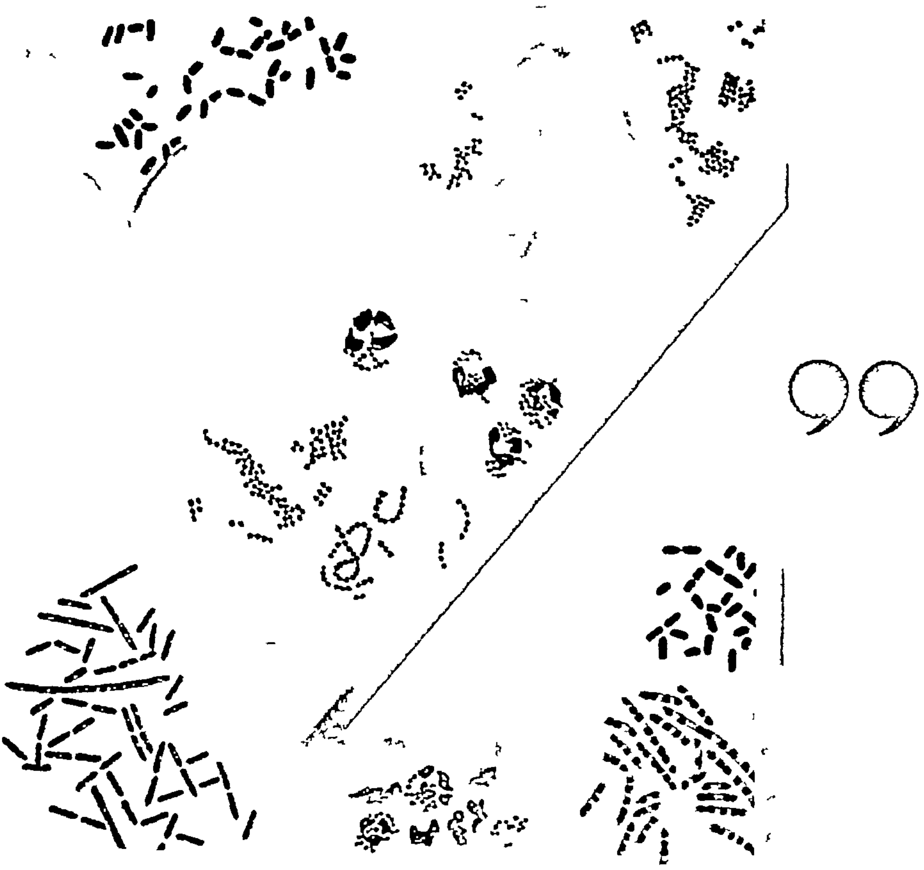

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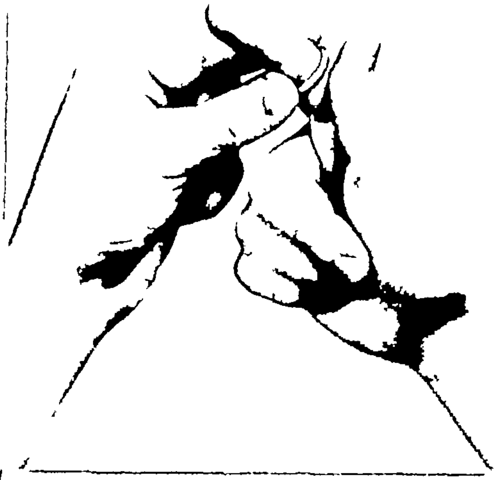

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Source—Malament, M J M Soc New Jersey *54* 115, 1957

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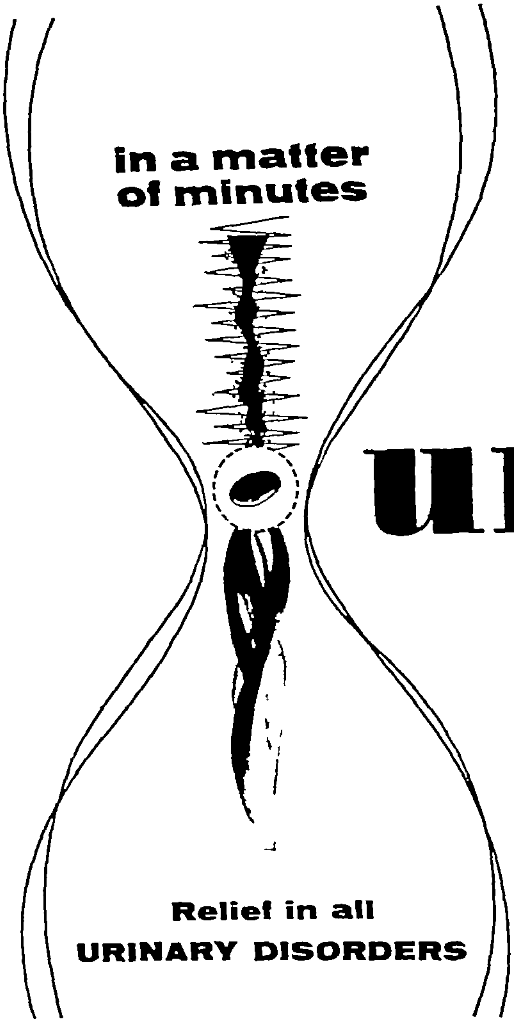

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[1] Strauss, B., Clin. Med., Vol. IV No 3 1957

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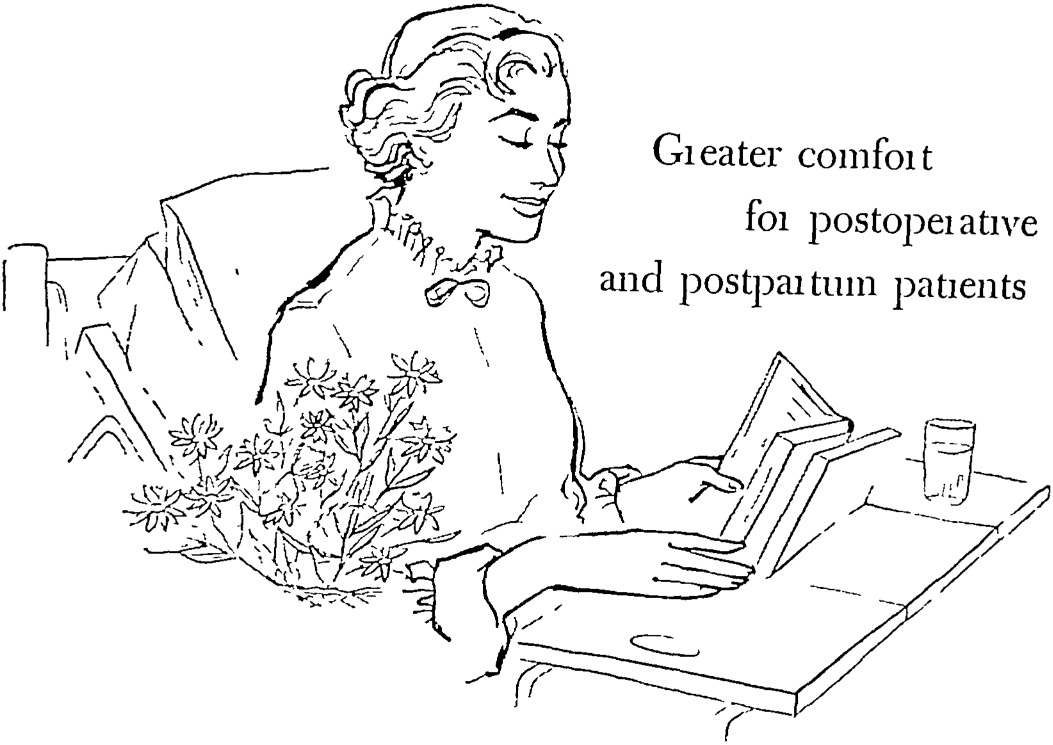

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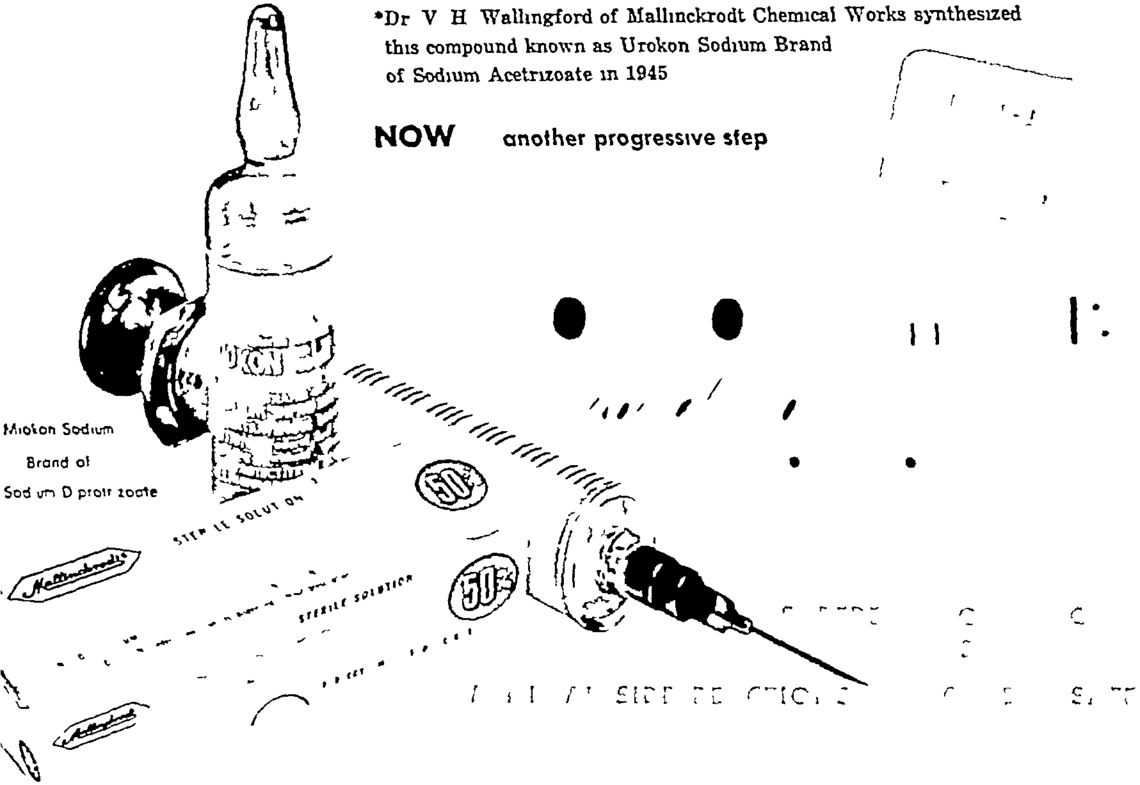

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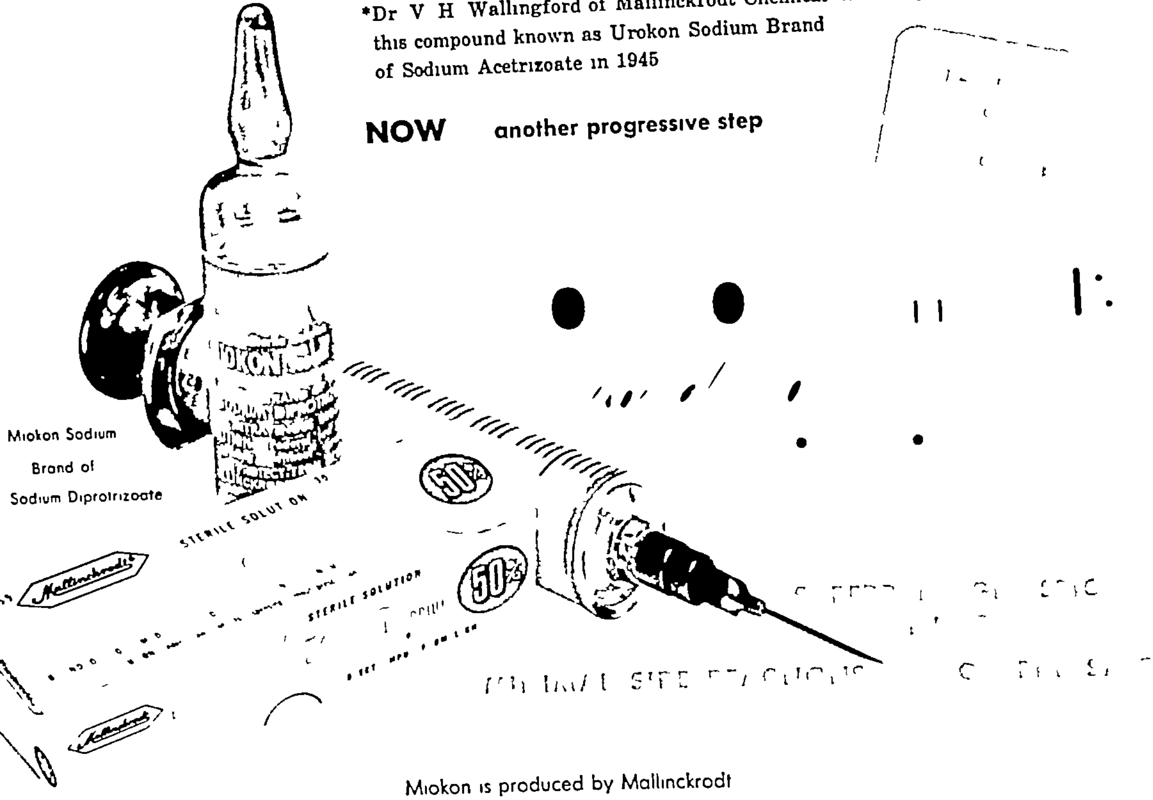

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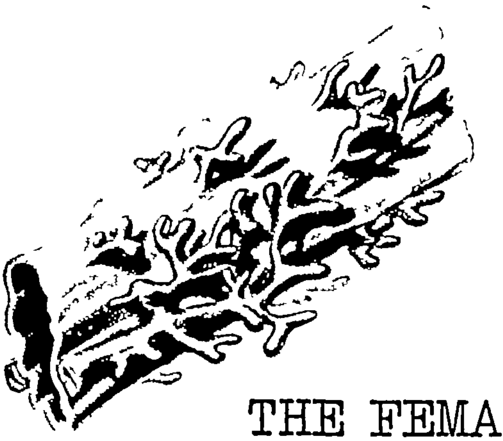

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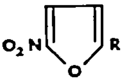
1 Wharton L R in Campbell M Urology Philadelphia and London, W B Saunders Company 1954 vol 2 p 1390 et seq
2 Barrett M E J M Ass Alabama 26 144 1956
3 Youngblood V H J Urol Balt 70 926 1953



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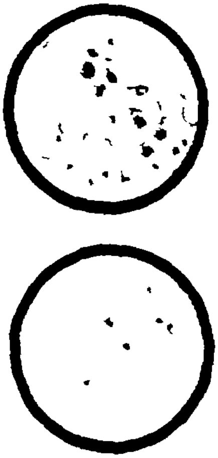

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[4] Youngblood V H Tomlin E M Williams J O and Kimmelstiel P Tr Southeast Sect Am Urol Ass (to be published) [5] Youngblood V H Tomlin E M and Davis J B J Urol Balt 78 150 1957

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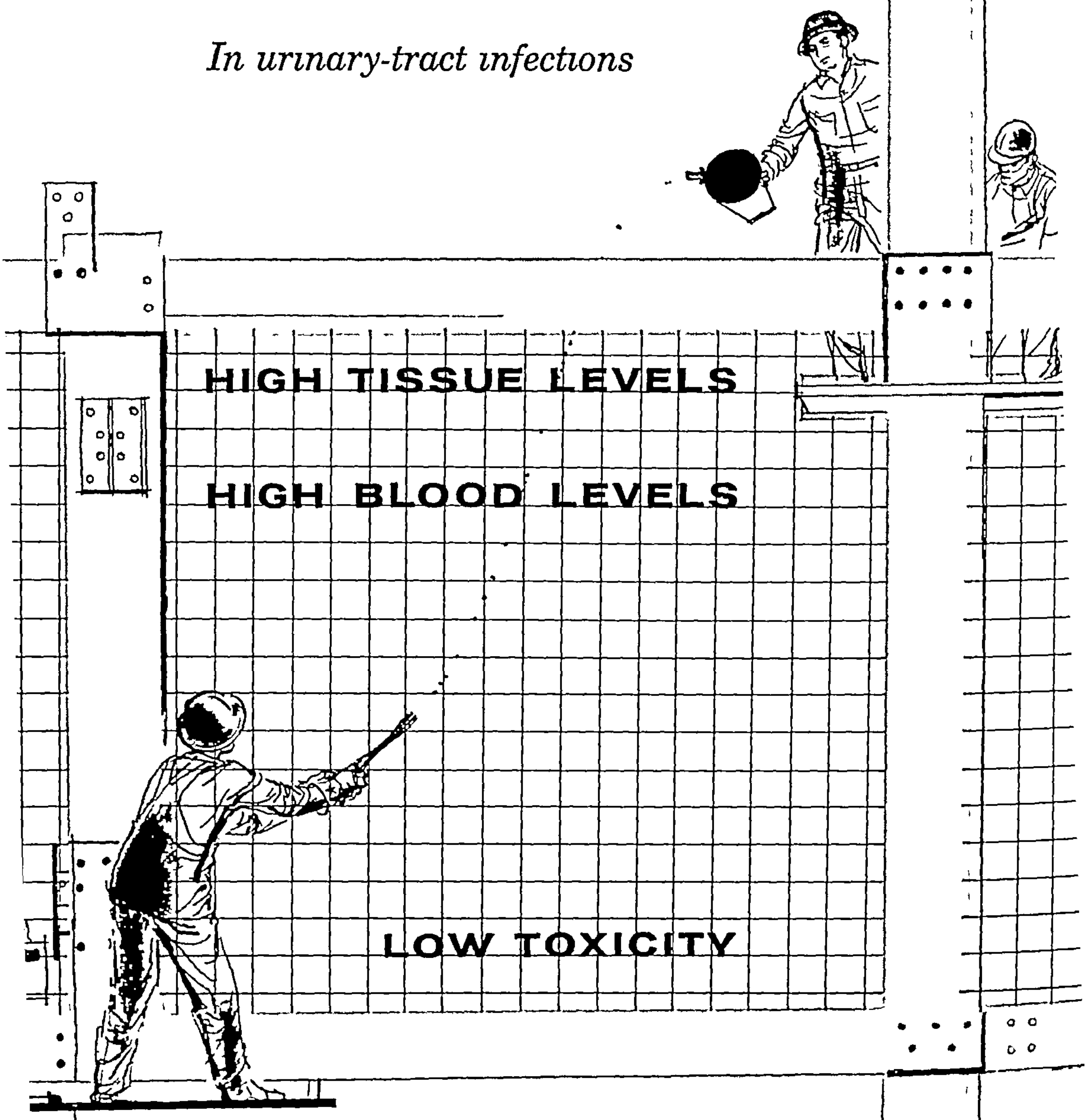
In urinary-tract infections



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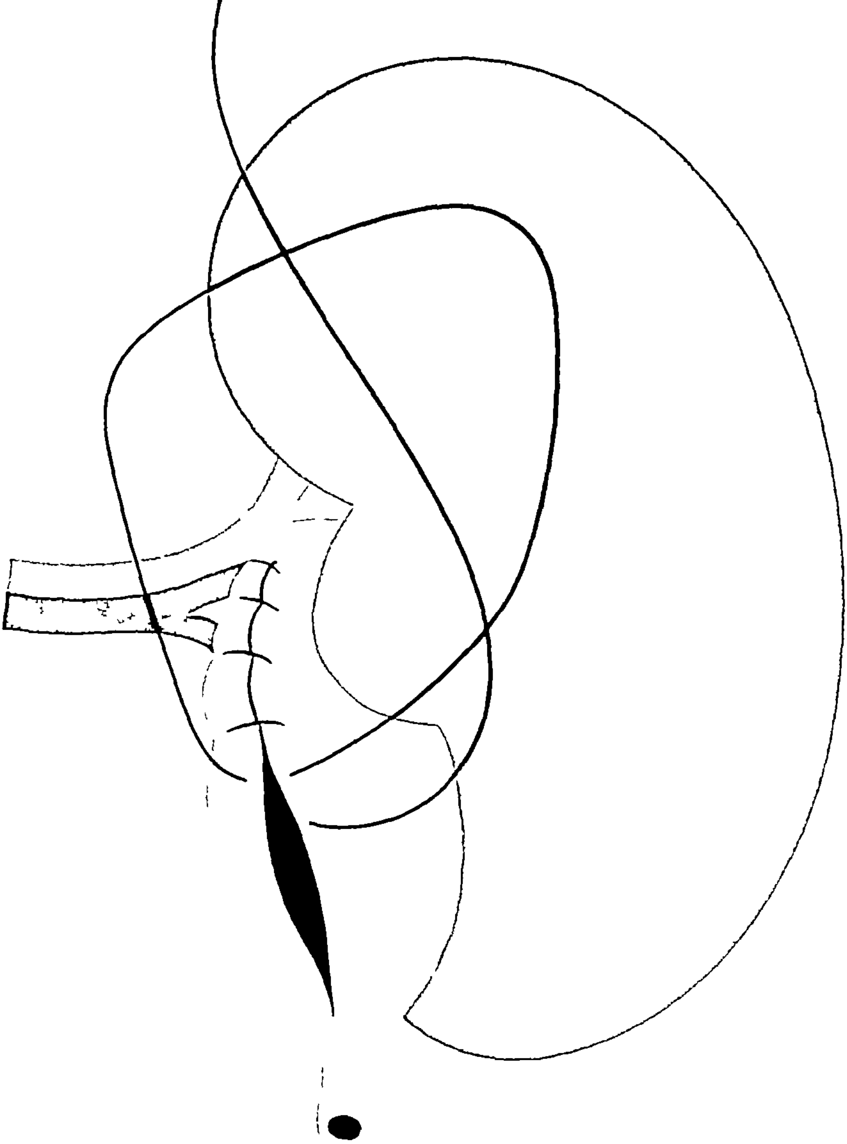

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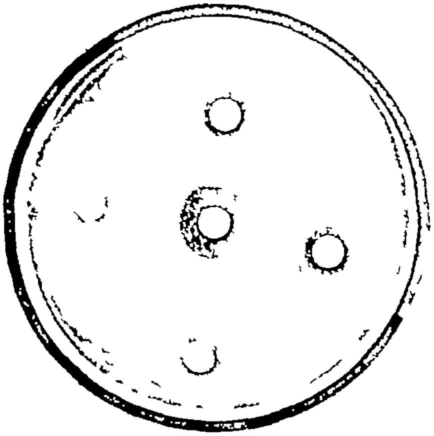

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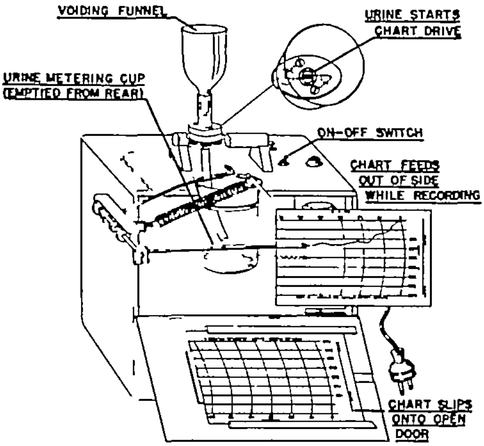
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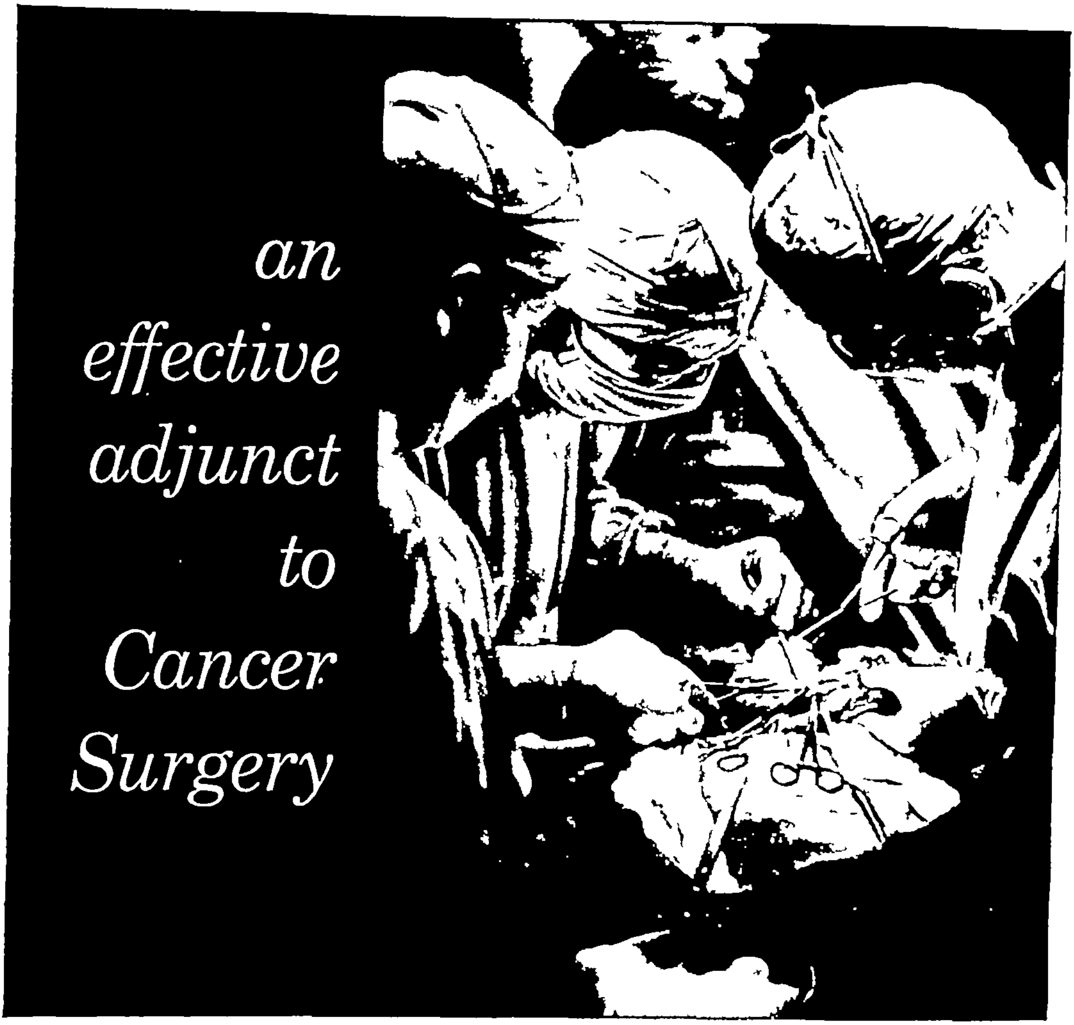

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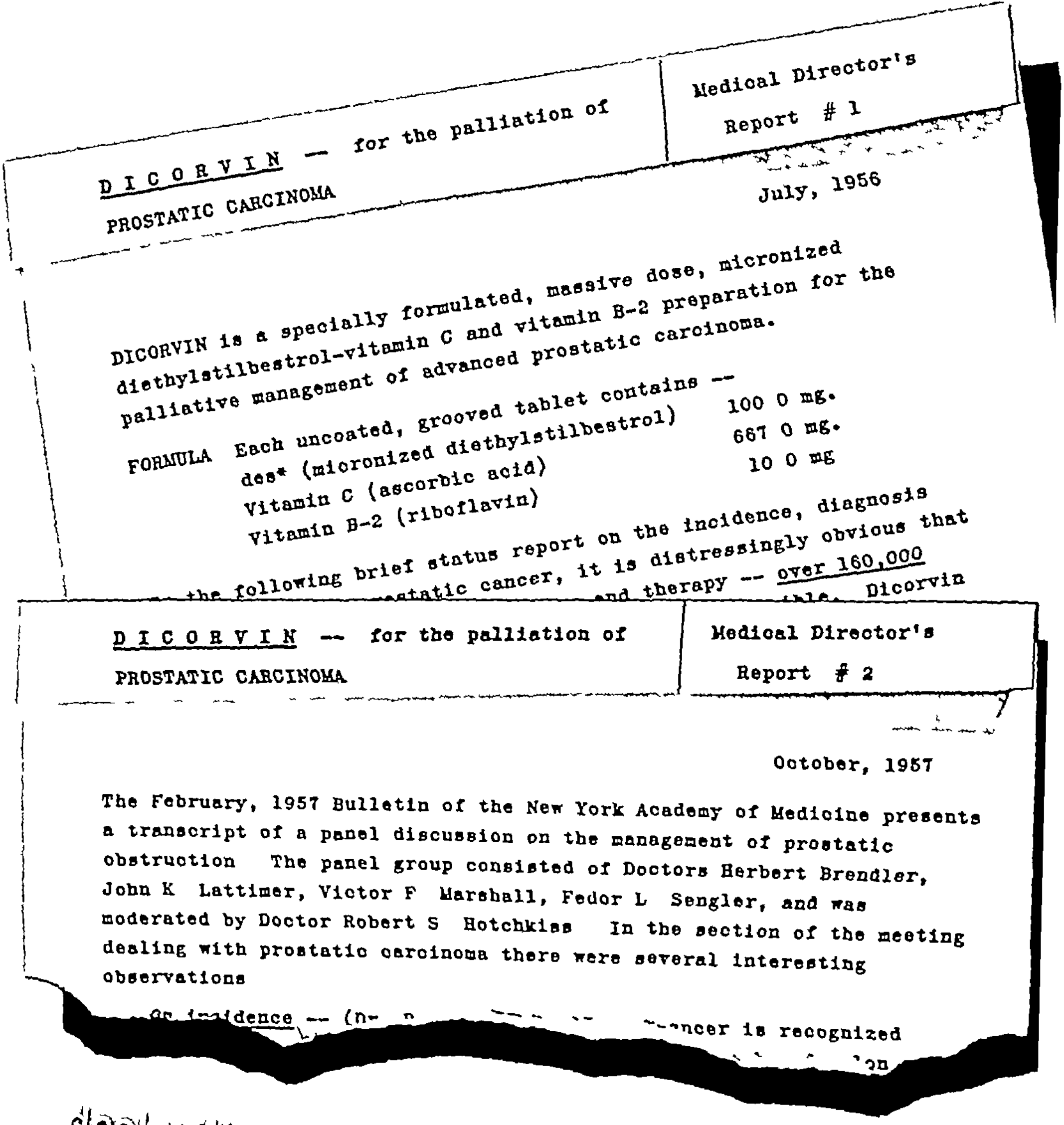

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---

D I C O R V I N -- for the palliation of PROSTATIC CARCINOMA

Medical Director's Report # 2

October, 1957

The February, 1957 Bulletin of the New York Academy of Medicine presents a transcript of a panel discussion on the management of prostatic obstruction The panel group consisted of Doctors Herbert Brendler, John K Lattimer, Victor F Marshall, Fedor L Sengler, and was moderated by Doctor Robert S Hotchkiss In the section of the meeting dealing with prostatic carcinoma there were several interesting observations

On incidence -- (n- [illegible] ncer is recognized

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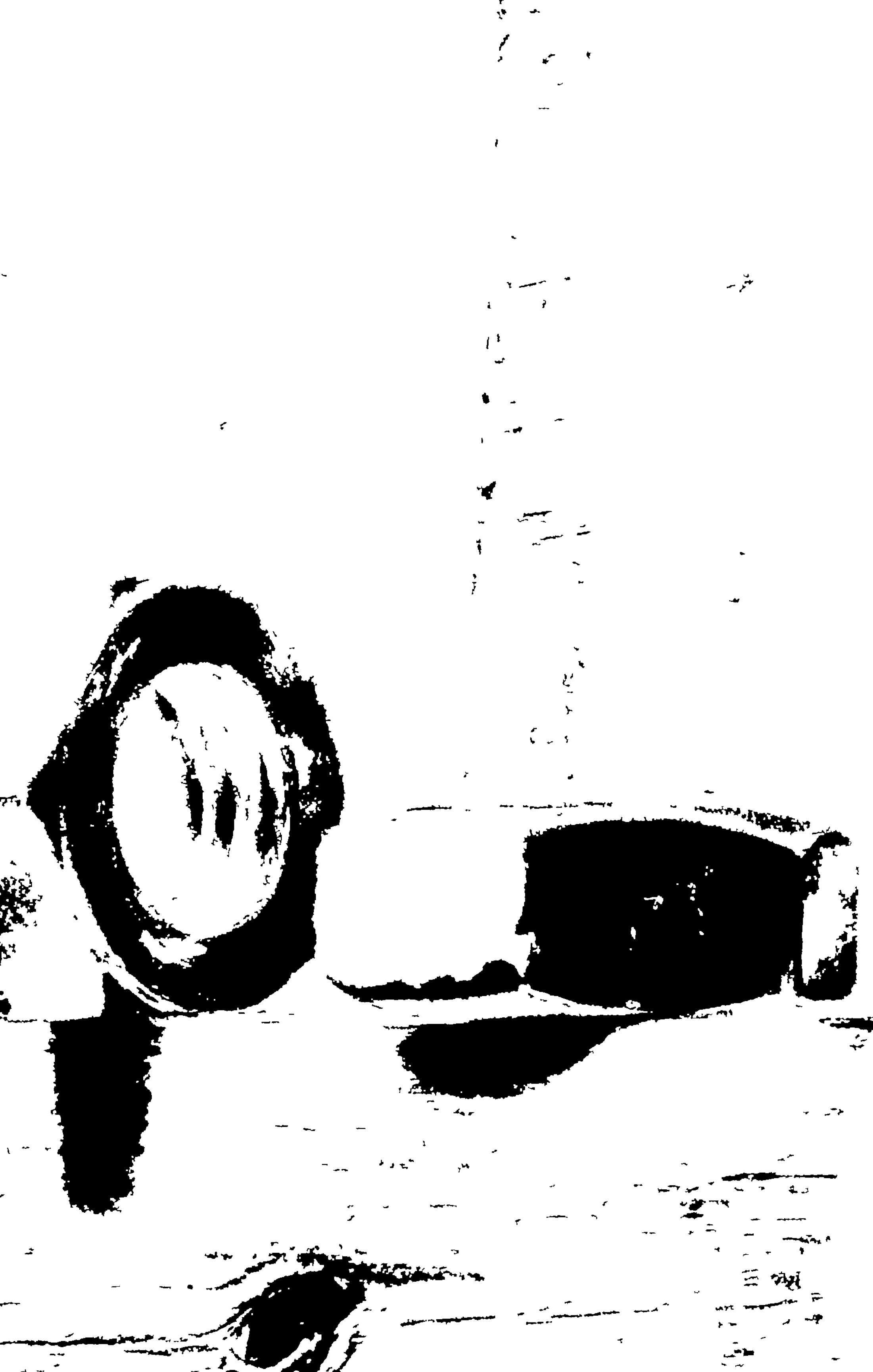

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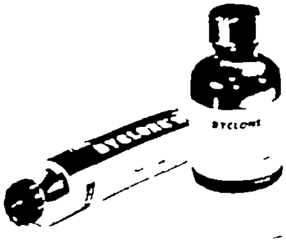

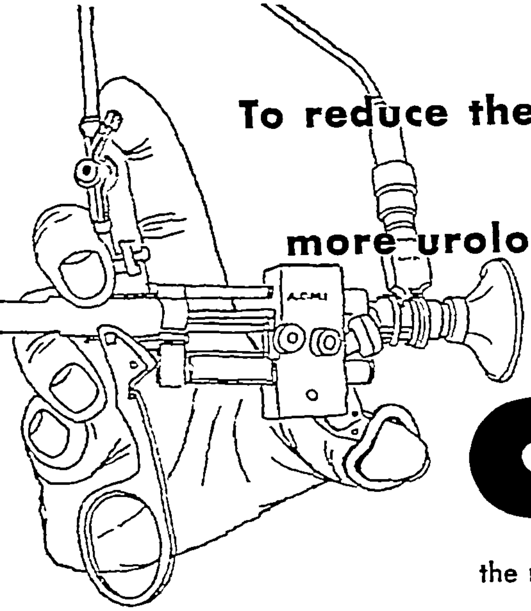

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1 Creevy C D Surgery 39 180 1956,
2. Schulte R. L. Hammer H J., and Reynolds. L. R. J Urology 71 656 1954

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*Rutenburg, A. M.: Ann. New York Acad. Sc. *69*:359 (Oct. 12) 1957

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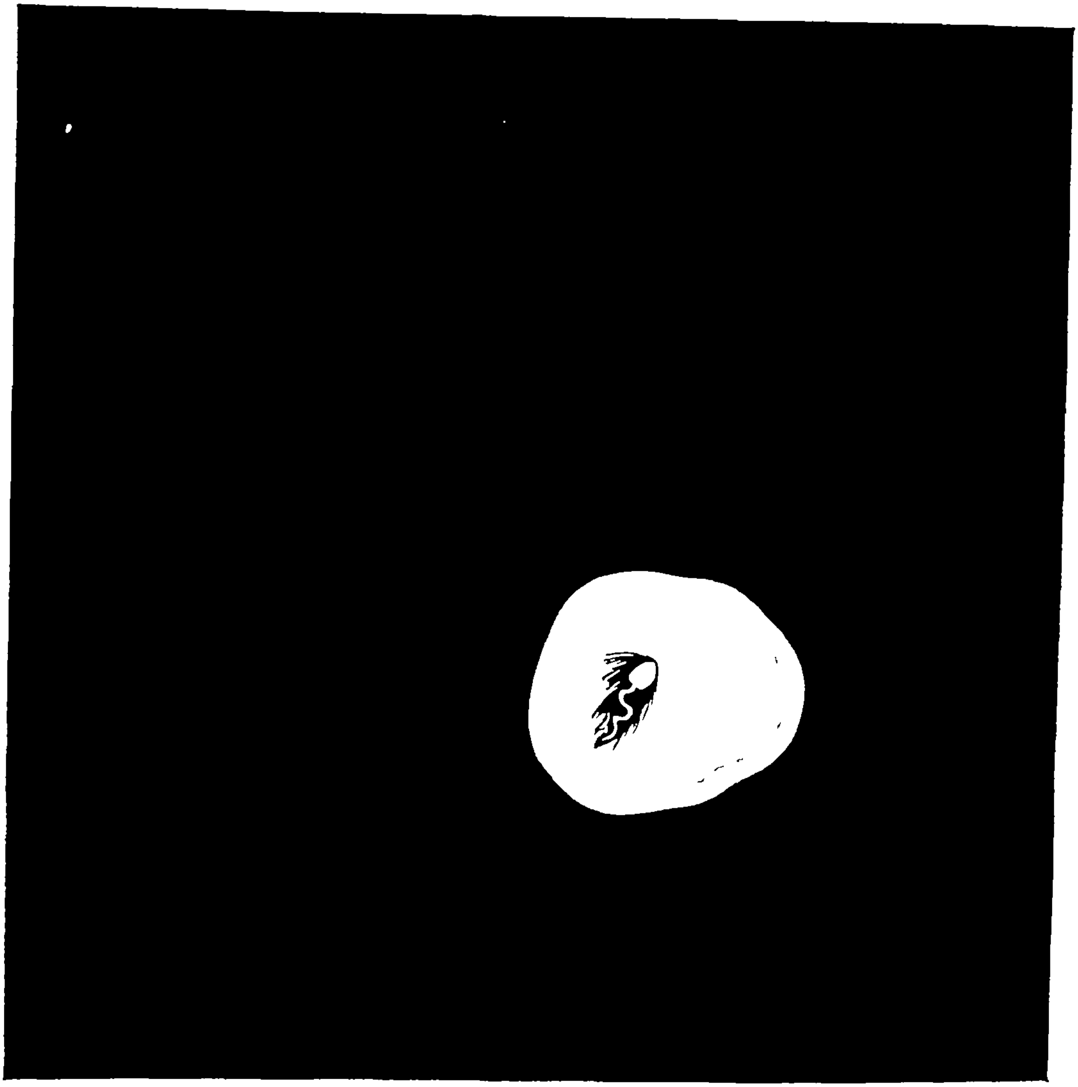

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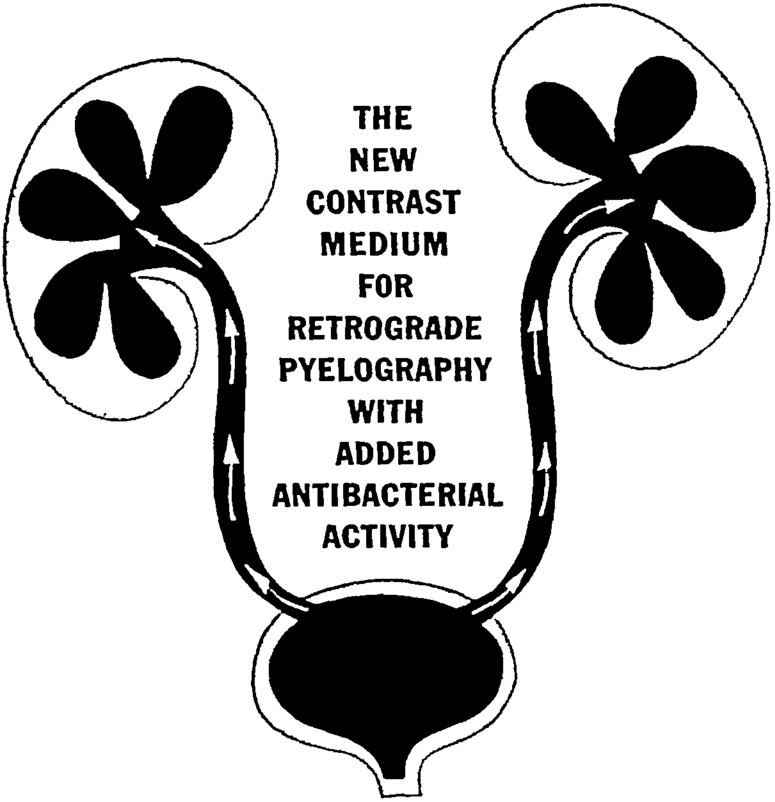

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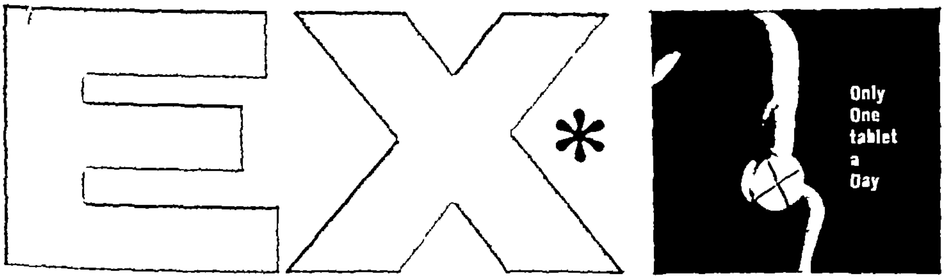

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References 1 Grieble, H C and Jackson G G Prolonged Treatment of Urinary Tract Infections with Sulfamethoxypyridazine *New England J Med* 258 1 7 1958 2 Editorial *New England J Med* 258 48-49 1958 3 Jones, W F Jr and Finland M Sulfamethoxypyridazine and Sulfachloropyridazine *Ann New York Acad Sc* 60 473-483 1957

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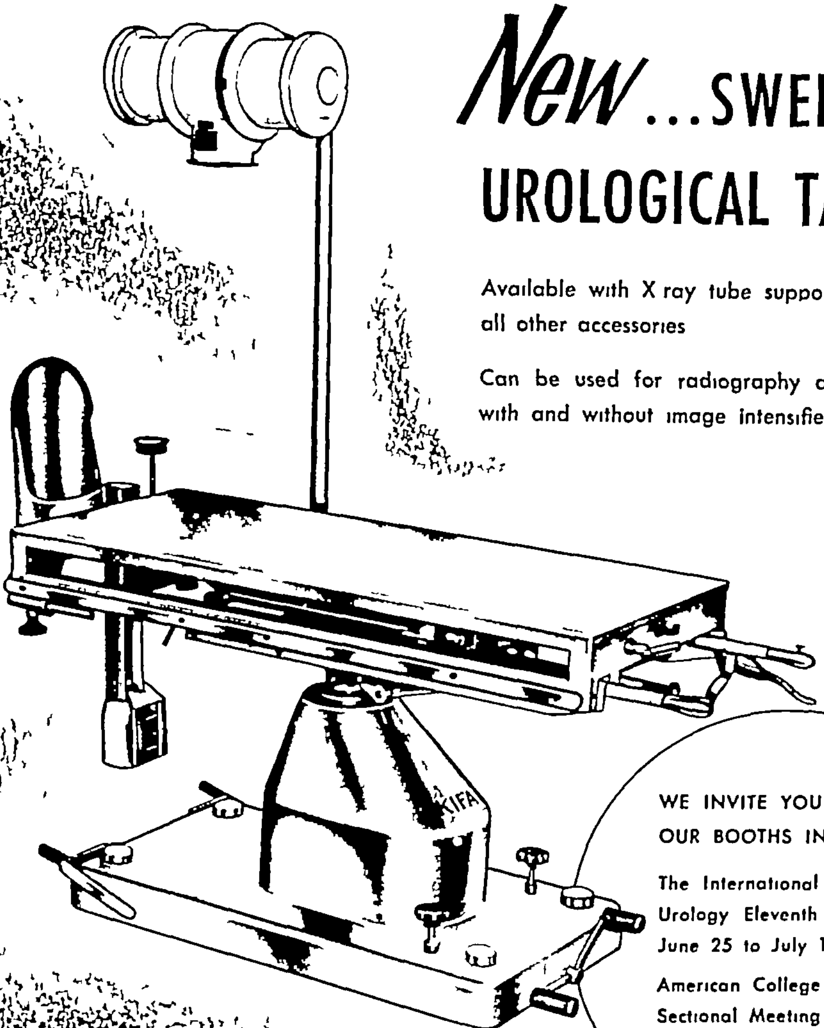

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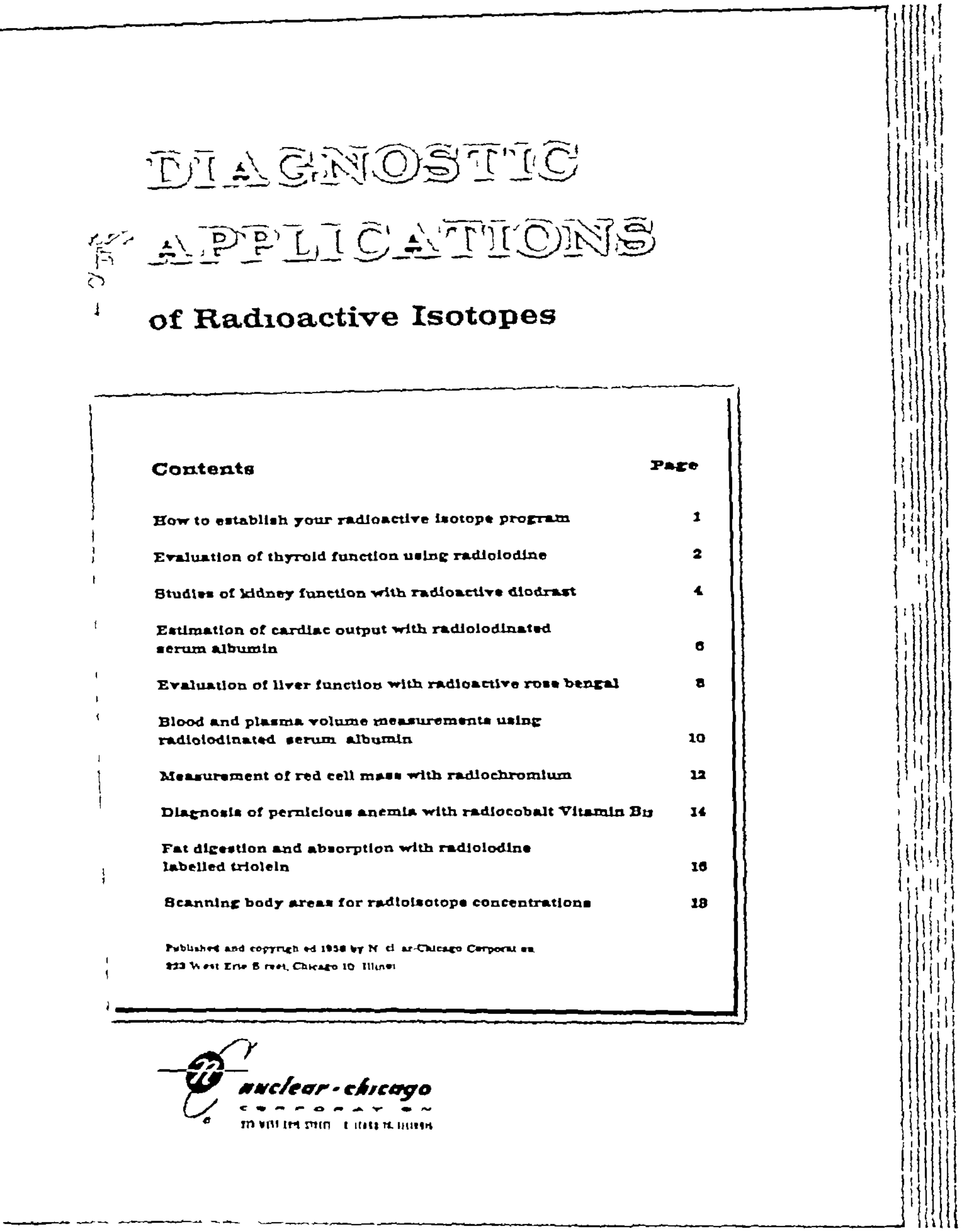

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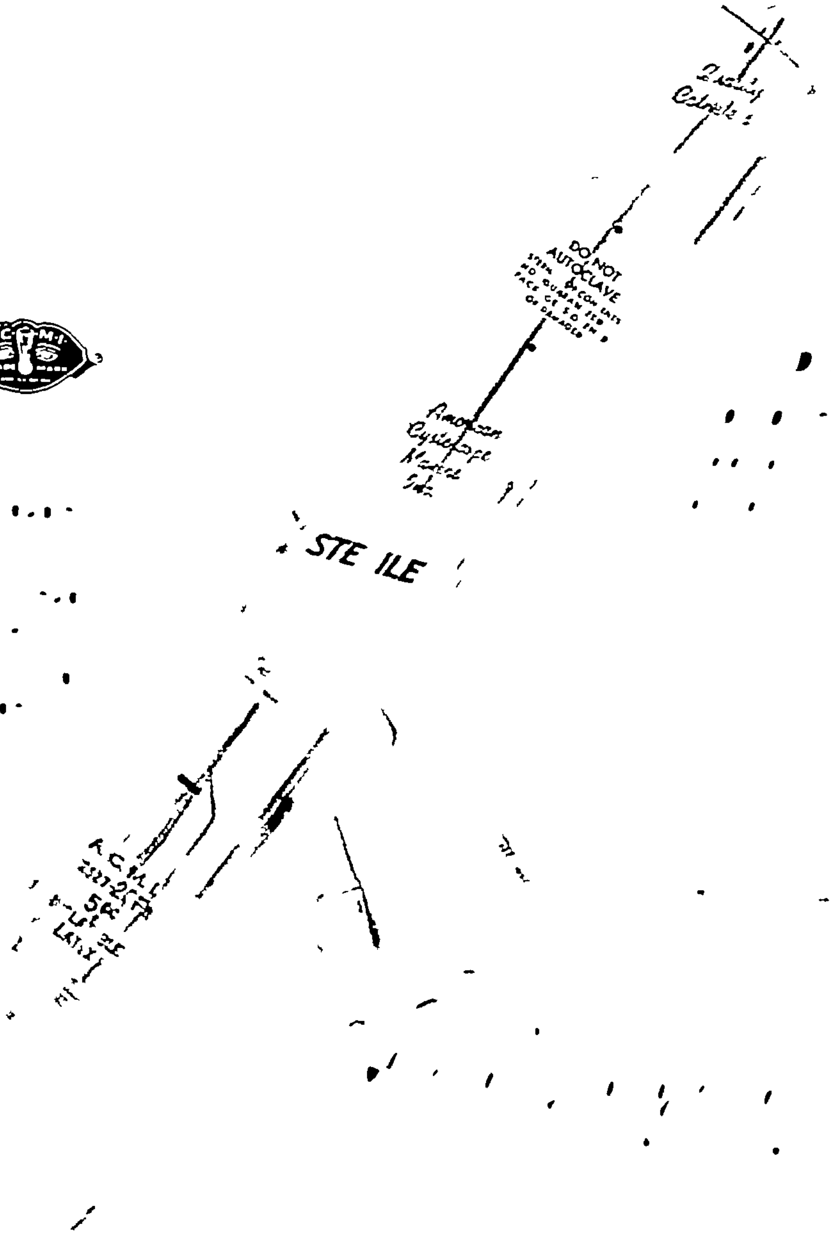
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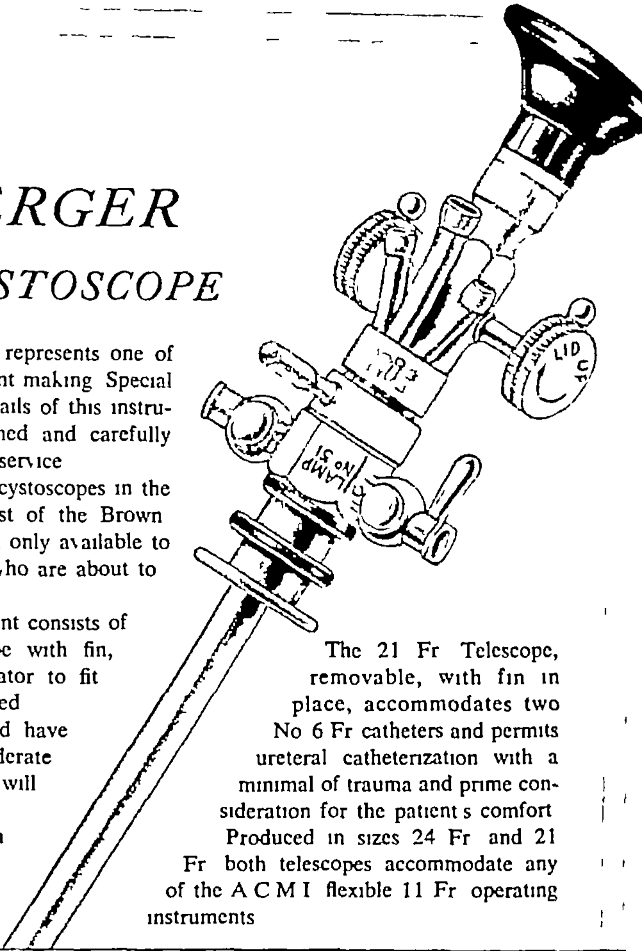

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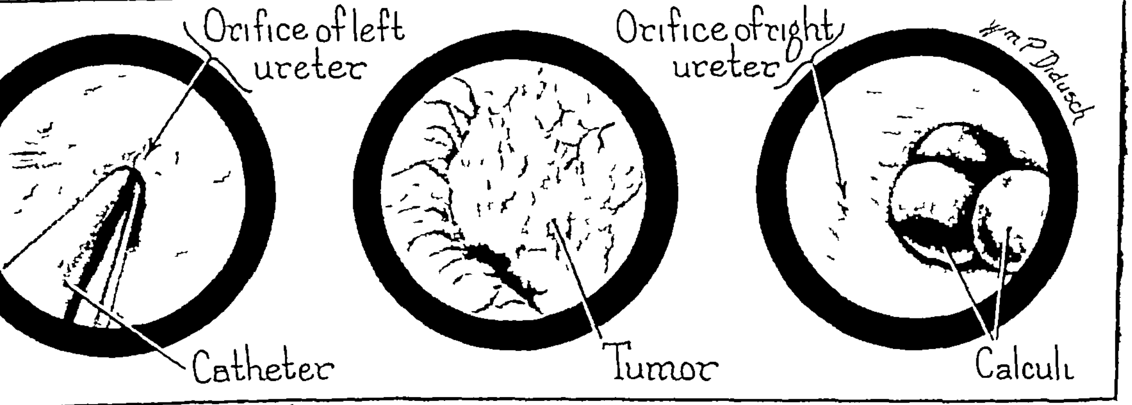

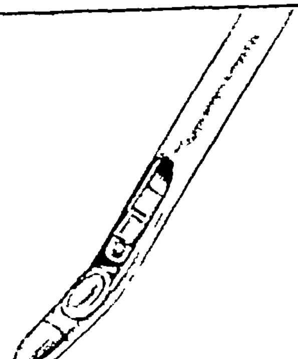

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THE JOURNAL OF UROLOGY
Vol. 79, No. 6, June 1958
Printed in U.S.A.

HETEROTOPIC OSSIFICATION IN THE ISCHEMIC KIDNEY OF THE RABBIT, RAT AND GUINEA PIG

J. B. BRIDGES

From the Anatomy Department, Queen's University, Belfast, North Ireland

It is well known that ligation of the renal vessels in the rabbit leads to bone formation in the ischemic kidney (Sacerdotti and Frattin, 1902, Pocharisski, 1905, Maximow, 1906, Liek, 1908, Asami and Dock, 1920), but so far this has not been reported in other animals. It has been suggested (Huggins, 1931) that surviving ureteric transitional epithelium may be responsible for initiating the bone formation, for ossification starts just beneath the transitional epithelium of the ureteric pelvis, and bone is found around grafts of bladder mucosa to the rectus sheath in dogs (Huggins, 1931), and cat (Johnson and McMinn, 1956), while Huggins, McCarroll and Blocksom (1936) reported similar findings in rats and guinea pigs, though Huggins (1931) was successful in one only of six bladder mucosal grafts in rabbits.

The hypothesis that the epithelium of the ureteric pelvis is responsible for inducing bone in the ischemic kidney of the rabbit evidently needs further investigation and it would help if the phenomenon could be studied in other animals also. It was decided, therefore, to look for bone induction after ligation of the renal vessels in the rat and guinea pig as well as the rabbit, and to study in detail the histological changes following ligation, in the hope of elucidating the role of the transitional epithelium. Ligation of the testicular and splenic vessels in the rabbit and rat was also carried out to see if bone formation could be induced by experimental ischemia in these organs also.

MATERIAL AND METHODS

Under ether anesthesia the kidney was exposed through a left dorsolumbar incision in 12 rabbits, 10 rats, and 8 guinea pigs. The ureter was carefully separated from the renal artery and vein, and these vessels were ligated with linen thread, the ureter not being included in the ligature. The kidney was then returned to the abdomen, and the wound closed in layers.

After periods varying from 4 up to 195 days the animals were killed. The kidney was dissected free from adhesions, removed, fixed in formol-saline, decalcified in 5 per cent trichloracetic acid, and embedded in paraffin wax. Sections were stained either with Weigert's iron hematoxylin and van Gieson or with Wilder's reticulin stain.

In 2 rabbits killed after 7 and 14 days, the entire animal was perfused with India ink immediately after death by means of a cannula inserted into the left ventricle. The kidney was then removed, dehydrated and embedded in celloidin. Sections cut at 30 μ were lightly counterstained with iron hematoxylin and van Gieson.

The kidney of another rabbit was removed after 40 days, fixed in neutralized

Accepted for publication December 27, 1957

80 per cent alcohol, dehydrated and embedded in celloidin Sections cut at 30 µ were examined for alkaline phosphatase activity by Gomori's (1939) original method, and by the azo-dye-coupling technique of Seligman and Manheimer (1949)

In 8 adult rabbits and 5 adult rats the testis was pushed out of the scrotum into the abdomen, exposed through a low midline incision, and then tight ligatures of linen thread were placed around the pedicles at its upper and lower poles before closing the wound Lastly, in 2 rabbits the splenic artery and vein were isolated through a left subcostal incision and ligated with linen thread One hundred days after operation all these animals were killed and the testis or spleen recovered and studied histologically

RESULTS

Ligation of renal vessels in the rabbit Kidneys recovered 4, 7 and 14 days after ligation were of normal size, dark red in color and of a soft, friable consistency Sections showed hyaline degeneration of the entire tubular system with some leukocytic accumulations beneath the capsule The transitional epithelium of the ureteric pelvis, however, stained normally Specimens injected 7 and 14 days after ligation showed a well vascularized zone in the immediate vicinity of the pelvis and small vessels entering the superficial part of the necrotic cortex from the capsule The three specimens examined after 40 days were small, pale and hard, and were gritty on sectioning The medulla was largely replaced by dense fibrous tissue, and this had begun to spread into the cortex between the necrotic tubules In the medulla especially there were accumulations of inflammatory cells Trabeculae of membrane bone were present in the fibrous tissue immediately beneath the transitional epithelium, which was thicker than normal and showed mitotic figures

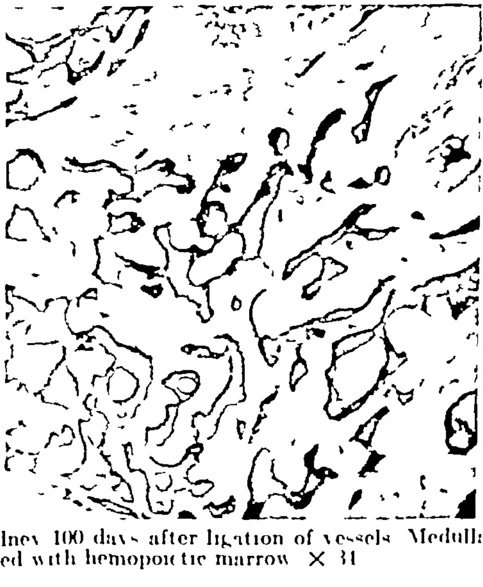

Fig 1 Rabbit kidney 100 days after ligation of vessels Medulla is replaced by bony trabeculae interspersed with hemopoietic marrow × 31

Intense alkaline phosphatase activity was present in the epithelium, in the cells around the bone and in a patch of fibrous tissue adjacent to the epithelium. In spite of the hardness of the organ, however, there was little evidence of calcification outside the bone.

After 70 days the kidney was small and stony hard. Bone was present just beneath the ureteric pelvis. The epithelium was hyperplastic and cords of cells could be seen extending from it into the fibrosed medulla. Hyalinized tubules were still present in the cortex, into which a few blood vessels had penetrated from the capsule.

After 80 days the medulla around the ureteric pelvis was replaced by cancellous

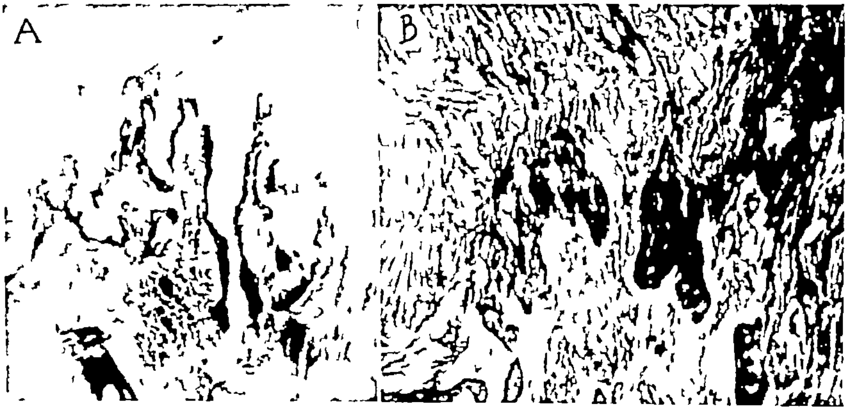

Fig. 2. Rabbit kidney 100 days after ligation of vessels. *A*, bone is seen incorporating collagenous fibers of renal cortex. *B*, bone formation extends into cortex resembling epiphyseal plate. × 100

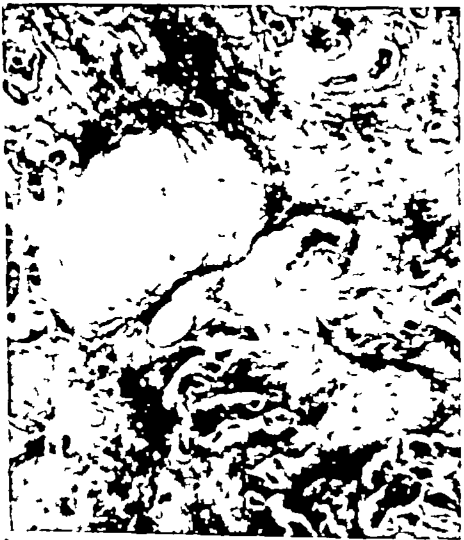

Fig. 3. Rabbit kidney 195 days after ligation of vessels. Several nodules of young cartilage are seen between cortical tubular remnants. × 100

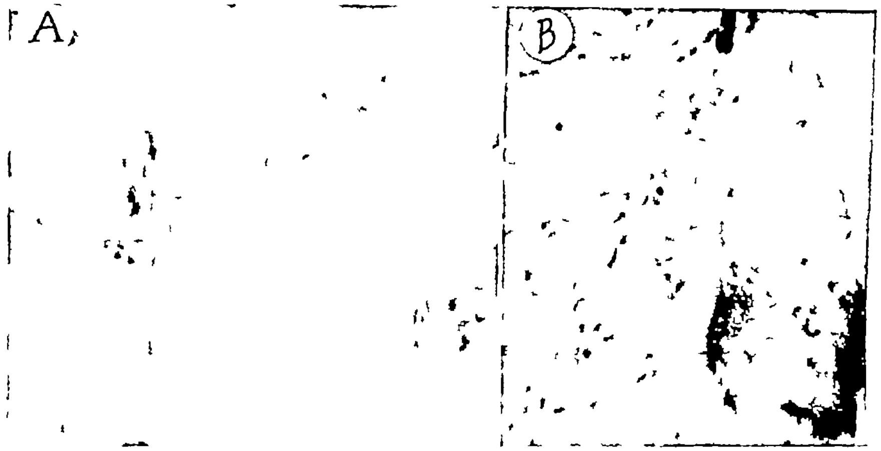

FIG 4 Rat kidney 80 days after ligation of vessels *A*, cords of transitional epithelial cells are seen apparently migrating into medulla *B*, same specimen as *A* shows bone induction at distance from ureteric epithelium but in close association with cluster of migrated transitional epithelial cells × 450

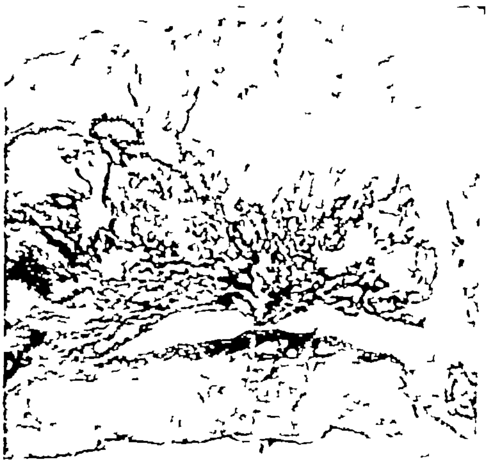

FIG 5 Rat kidney 140 days after ligation of vessels Bone formation is well established in medulla and extends into cortical zone × 15

bone containing hemopoietic marrow, the rest of the medulla and much of the cortex being occupied by dense fibrous tissue Residual tubules were undergoing erosion by multinucleated giant cells

After 100 days (2 specimens) the medulla had been completely replaced by an ossicle of bone with haversian systems and hemopoietic marrow (fig 1*) Bone was also extending out into the cortex, invading dense fibrous tissue in some places (fig 2, *B*†), and masses of calcified hyalinized tubules in others (fig 2, *A*) The advance of ossification into the latter resembled endochondral ossification, the calcified tubules playing the role of calcified cartilage

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* Weigert's iron hematoxylin and van Gieson stain
† Wilder's reticulin stain

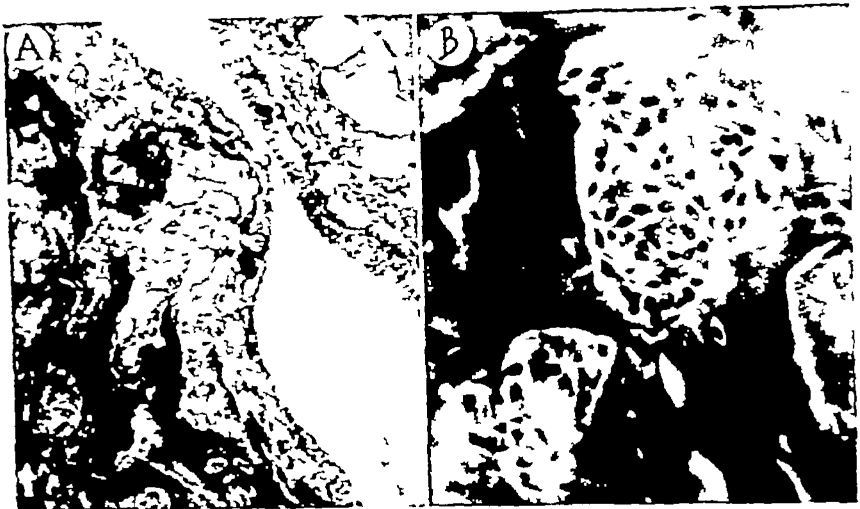

FIG 6 Same specimen as figure 5 A, closeness of persisting transitional epithelium of ureteric pelvis to induced bone is seen B, cords of migrated transitional epithelial cells are seen within haversian systems of bone in close proximity to osteogenic cells lining bony surfaces × 450

After 195 days (2 specimens) the kidneys consisted chiefly of dense vascularized fibrous tissue and tubular remnants The few bony spicules present were undergoing osteoclasis In one of the specimens however young cartilage was seen in the form of isolated nodules within the fibrous tissue near the bone (fig 3*) The transitional epithelium still stained normally and contained mitotic figures

Ligation of renal vessels in the rat After 40 days (2 specimens) the kidneys were very similar to those of the rabbit at the same stage except that no bone was present

After 70 days however, all three specimens showed varying amounts of bone with hemopoietic marrow which had partly replaced the medulla and was extending into the cortex in the wake of dense fibrous tissue

After 80 days the two specimens both showed bone formation In one cords of epithelial cells were seen extending into the medulla from the lining of the ureteric pelvis (fig 4 A*), and isolated pieces of bone had formed very close to some of these (fig 4 B*) Bone was also present in the kidney at 100 days but this specimen was complicated by the presence of an abscess at the upper pole

At 140 days (2 specimens) bone had replaced the medulla and much of the fibrosed cortex (fig 5*) The epithelium of the ureteric pelvis was thickened and cords of cells extended from it into the interstices of the adjacent cancellous bone (fig 6*)

Ligation of renal vessels in the guinea pig Without exception the kidneys became grossly infected and were largely replaced by abscesses However the transitional epithelium survived and stained normally In two specimens after 100 days bone was present in a relatively thick zone beneath the epithelium

* Weigert's iron hematoxylin and van Gieson stain

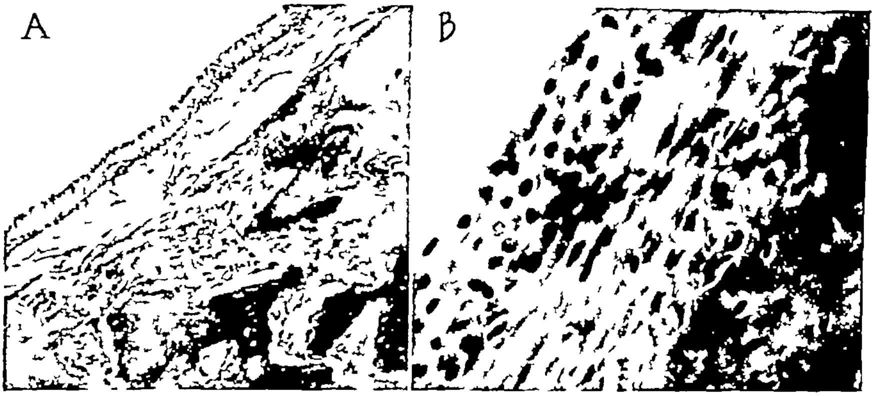

FIG 7 Guinea pig kidney 100 days after ligation of vessels *A*, bone formation seen in renal medulla, beneath persisting transitional epithelium of ureteric pelvis *B*, transitional epithelial cells of ureteric pelvis are separated from osteogenic cells lining bone surface by layer of spindle shaped cells which serve as periosteum × 450

(fig 7, *A**), separated from it only by a very thin layer of fibrous tissue which served as a periosteum (fig 7, *B**)

Ligation of testicular and splenic vessles After 100 days the testes consisted of hyalinized tubules surrounded by dense fibrous tissue, while the spleens were almost completely necrotic No bone or cartilage was observed in either organ

DISCUSSION

These experiments have shown that bone formation follows ligation of the renal vessels as consistently in the rat as in the rabbit, and the histological changes are similar in the two animals For some reason the guinea pig kidneys all became infected, but in spite of this bone was found in two cases The main histological features were hyperplasia of the ureteric epithelium with a tendency for it to invade the medulla, hyaline necrosis of the entire tubular system, progressive fibrosis accompanying revascularization, and bone formation beginning just beneath the epithelium and spreading through the medulla and into the cortex, replacing fibrous tissue and calcified tubules along a broad front The bone was formed directly in membrane, cartilage being found only in one very late specimen after most of the bone had been resorbed Moreover, the bone underwent gradual reorganization, developing haversian systems and a hemopoietic marrow The transitional epithelium and the fibrous tissue immediately beneath it evidently survived owing to its independent blood supply from the ureteric vessels which were not ligated The fact that bone always began to form either immediately beneath the epithelium, or else in very close proximity to cords of invading epithelial cells derived from it, strongly suggests a causal relationship between the epithelium and bone formation The alternative suggestion that the course of ossification simply follows the pattern of revascularization and that its association with the epithelium is coincidental, is ruled out by the absence of bone formation around the capsular blood vessels invading the cortex It seems

* Weigert's iron hematoxylin and van Gieson stain

likely, therefore, that the epithelium is responsible for inducing the transformation of subjacent fibroblasts into osteoblasts In this connection it is pertinent to report that in current experiments intramembranous ossification has been induced under the kidney capsule in the rabbit following the implantation of fragments of living bladder mucosa, though, surprisingly, alcohol-fixed implants of bladder mucosa in this situation first induced cartilage which was later replaced by bone (Bridges and Pritchard, 1958)

Why ossification does not occur in the normal kidney in these animals is difficult to answer Possibly preliminary hyperplastic changes in the transitional epithelium are necessary, for in transplants of the epithelium to the rectus sheath in other animals bone is only induced near proliferating and actively migrating epithelium (Huggins, 1931, Huggins and associates, 1936, Johnson and McMinn, 1956) It may be that the experimental ischemia changed the character of the fibrous tissue, enabling it to respond to the bone-inductor, or chemical substances accumulating in the necrotic kidney may play an essential part Liek (1908), for example, believed that the accumulation of calcium salts stimulated bone formation, but the weight of evidence is against this (Asami and Dock, 1920, Huggins and associates, 1936)

The origin of the hemopoietic bone marrow is a separate problem, but apart from the fact that induced bone anywhere tends to become organized into a marrow-filled ossicle, nothing is known of its genesis The formation of cartilage in one specimen is worthy of passing reference for it has never been previously reported It is possibly an alternative induction produced in areas where the blood supply is inadequate for bone formation (Ham, 1930) While the transitional epithelium inductor does not at present seem very relevant to the general problem of the role of induction in normal bone growth and repair (although Copher and Key (1934) and Copher, Key and West (1932) have attempted to modify fracture repair in dogs with transplants and extracts of bladder mucosa), nevertheless it provides an experimental method of inducing heterotopic ossification

The principal conclusions drawn from this study are that bone forms in ischemic kidneys in rats and guinea pigs as well as rabbits, and that an inducing agent released from hyperplastic transitional epithelium is responsible for initiating ossification

The author's gratitude is due to Professor J J Pritchard for criticism and advice and to Miss A O'Hare for technical assistance He would also like to express his thanks to the Queen's University, Belfast, for a grant from their research fund towards the cost of accomplishing this work

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ACETYLSALICYLIC ACID AND SALICYLAMIDE EFFECT ON RENAL CALCULOSIS IN PATIENTS WITH SPINAL CORD INJURY

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One of the prominent complications of spinal cord injuries is that of renal calculosis. Of the 1006 patients with traumatic cord lesions at this hospital up to May of 1955, 69 (6.8 per cent) had renal calculi and up to May 1957 100 (8.4 per cent) out of a total of 1187 patients had calculi. While hospitalized, a large fluid intake and weight bearing (braces, parallel bars, tilt table) are stressed as a means of reducing the incidence of calculosis. Few patients, however, follow these dicta after discharge from the hospital; hence, any procedure that could be easily adhered to, and which would either prevent the formation of calculi or the growth of existing stones, would be useful in the care of these patients. The reports of Prien and Walker on the beneficial effect of salicylates in impeding the formation of calcium phosphate calculi appeared sufficiently promising as to warrant a trial in a group of our patients, first because of the simplicity of the regimen and secondly because the stones removed from these patients consisted chemically of a mixture of calcium phosphate (carboxyl apatite) and magnesium ammonium phosphate, i.e., that type of stones which reportedly were slowed in their growth by the use of salicylates.

METHODS AND MATERIALS

Fifteen male patients aged 24 to 42 were chosen for the study with no regard to level of spinal lesion or elapsed period of time since their injury which varied from 16 to 138 months. Twelve of the group had cervical lesions while three had lesions at D-4, D-7 and L-1 respectively. All patients had either passed stones spontaneously, had them surgically removed previously or had them in situ at the start of this study. All of the group had infected and strongly alkaline urine. The predominant organism was Proteus vulgaris followed by Pseudomonas aeruginosa, Aerobacter aerogenes, Paracolon and Staphylococcus. Most of the organisms were relatively insensitive to the antibacterial agents.

For purposes of treatment six of the patients received aspirin gr. 10 t.i.d. for periods varying from 3 to 11 months and nine were given salicylamide gr. 10 t.i.d. for the same period of time. X-rays were compared before and after therapy. Twenty four hour urine collections were made for three days prior to starting drug therapy and at weekly intervals thereafter for the determination of glucuronic acid excretion. Glucuronic acid was determined by the method of Fishman and associates. Except for encouraging large fluid intakes no dietary control was exercised.

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ACETYLSALICYLIC ACID AND SALICYLAMIDE: EFFECT ON RENAL CALCULOSIS IN PATIENTS WITH SPINAL CORD INJURY

A. ESTIN COMARR AND HERBERT [illegible]

[illegible]

One of the prominent complications of spinal cord injuries is [illegible] of renal calculi. Of [illegible] patients with traumatic [illegible] 1945 [illegible] per cent had renal calculi, and up to May 1957 [illegible] per cent [illegible] patients had calculi. While a [illegible] fluid intake and [illegible] are [illegible] means of reducing the incidence of calculosis, few patients however follow these directions after discharge from the hospital. [illegible] any procedure that would be easily adhered to, and which would either prevent the formation of calculi or the growth of existing stones, would be useful in the care of these patients. The reports of Prien and Walker on the beneficial effect of salicylates in impeding the formation of calcium phosphate calculi appeared sufficiently promising as to warrant a trial in a group of our patients. [illegible] because of the simplicity of the regimen and [illegible] because most of the calculi removed from these patients consisted essentially of a mixture of calcium phosphate, [illegible] apatite, and magnesium ammonium phosphate, [illegible] this type of stone [illegible] the use of salicylates.

METHODS AND MATERIALS

Fifteen male patients aged [illegible] were chosen for this study with no regard to level of spinal cord injury [illegible]. Three of the group had cervical lesions while three had lesions at D-[illegible], D-7 and L-[illegible], respectively. All patients had either passed stones spontaneously, had them surgically removed previously, or had them at start of this study. [illegible] The predominant organism was Proteus vulgaris, followed by Pseudomonas aeruginosa, A. aerogenes, E. coli, Paracolon and Staph. aureus. Most of the organisms were relatively resistant to the antibacterial agents.

For purposes of treatment, [illegible] of the patients received aspirin gr. 10 [illegible] for periods varying from 3 to 11 months, and [illegible] were given salicylamide gr. 10 [illegible]. X-rays were compared before and after therapy. [illegible] determinations were made [illegible] of [illegible] Grammer [illegible] the method of Fiske [illegible].

Accepted for publication [illegible]

RESULTS

Of the patients for whom aspirin was prescribed only one, a patient with a cervical lesion who had passed a stone spontaneously prior to receiving the drug, showed no new stone formation or increase in size of existing stones He received the drug for eleven months During this period, his glucuronic acid excretion rose from an initial mean of 450 mg /24 hours to a mean of 1100 mg /24 hours The other five patients experienced continual growth of existing stones or formed new stones as follows

Patient E M , with a cervical lesion and no prior renal surgery, had a stone 16 mm by 3 mm on the right side at the start of treatment After 11 months of therapy the stone increased to 30 mm by 15 mm The initial mean glucuronic acid excretion of 920 mg /24 hours increased to a mean of 1600 mg /24 hours under therapy

Patient, S R , with a cervical lesion and no prior renal surgery, had a right single stone of 10 mm diameter, which after 11 months of treatment grew only slightly, but during the same period another stone appeared and grew to 10 mm

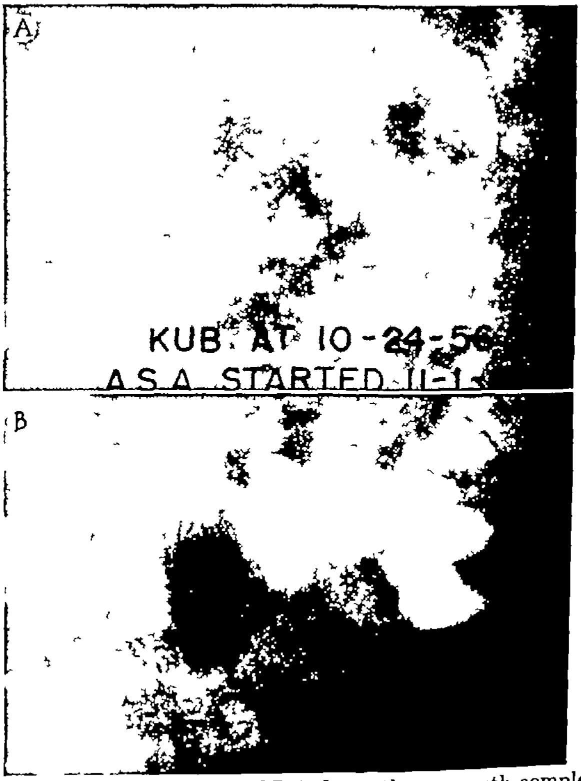

Fig 1 W V , man aged 35 Fracture of L 1, 8 months ago, with complete flaccid paraplegia below L 1 *A*, small stone fragment left behind at surgery increased to size shown in film, which was taken before aspirin therapy was instituted *B*, within 3 months of therapy original stone had enlarged to size shown in film

by 18 mm The initial mean glucuronic acid excretion was 650 mg /24 hours which increased to 1400 mg /24 hours while receiving the drug

Patient W V , with a lesion at L-1, had a postoperative calculus fragment on the left side which had grown to 25 mm by 15 mm Within three months' treatment, the stone had grown to staghorn size The initial mean glucuronic acid excretion was 425 mg /24 hours which increased to 800 mg /24 hours on therapy (fig 1)

Patient R S with a lesion at T-4 and no prior renal surgery, had a left renal stone 8 mm by 6 mm at the start of treatment which increased to 20 mm by 12 mm after 11 months of therapy The initial mean level of glucuronic acid excretion of 1500 mg /24 hours was not increased by the dosage of aspirin used (fig 2)

Patient T S , with a cervical lesion and no prior renal surgery, had a right renal stone 9 mm in diameter which grew to 12 mm after 6 months of treatment During the same period a new stone appeared and grew to 5 mm in diameter on the left side At the end of the six month period the right kidney was surgically

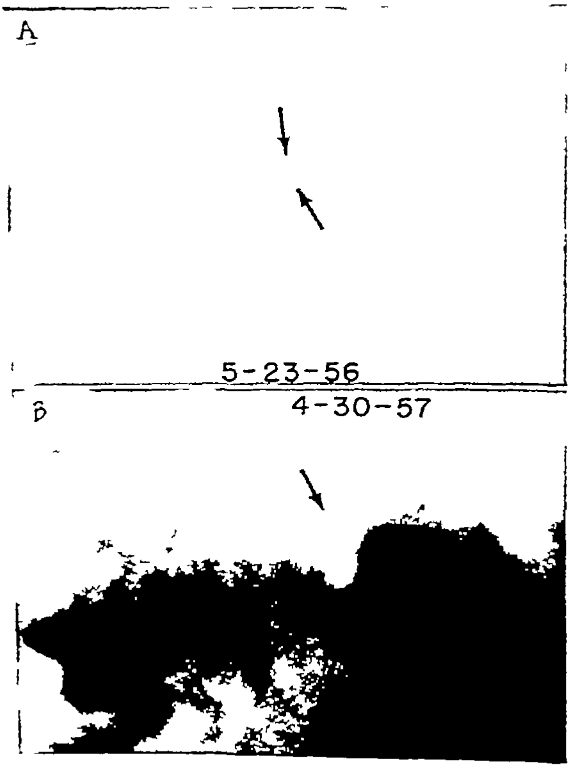

FIG 2 R S man aged 41 Fracture of T-4 22 months ago with complete spastic paralysis below T-4 Patient had not undergone prior surgery *A* film taken before aspirin therapy instituted *B* within 11 months of therapy original stone had enlarged to size shown in film

removed because of fulminating pyelonephritis which at the time of surgery had the gross appearance of hypernephroma The initial mean value of glucuronic acid excretion was 1300 mg /24 hours which was not increased by the dosage of aspirin given

Of the nine patients who received salicylamide, four with cervical lesions and previous renal surgery for calculosis remained stone free, while two other patients with cervical lesions, one with a 3 mm stone on the left side and one with a stone fragment following surgery on the right side, showed no additional growth during periods of drug therapy, varying from three to eleven months The initial mean glucuronic acid excretion in this group varied from 200–450 mg /24 hours and increased to mean values of 800–1300 mg /24 hours while receiving the drug The remaining three patients receiving salicylamide, however, had an increased stone growth as follows

Patient J L , with a cervical lesion and previous bilateral renal surgery had two 6 mm diameter stones on the left side prior to therapy, which grew to staghorn size within nine months of treatment During the same period, a new stone appeared in the right kidney and grew to staghorn size The initial mean glucuronic

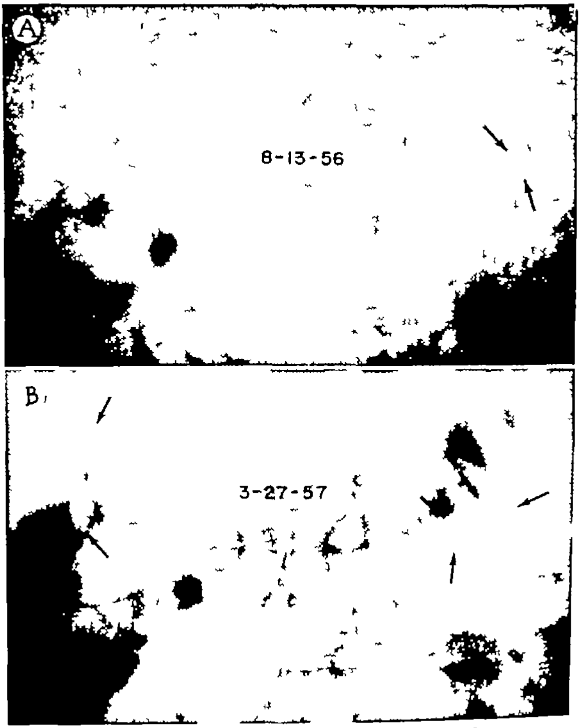

FIG 3 J G , man aged 24 Fracture of C 6, 20 months previously with complate spastic paralysis below C-6 Patient had not undergone prior surgery *A*, film taken before salicylamide therapy was instituted *B*, within 7 months of therapy, original stone on left side had grown and, in addition, another stone developed in same kidney, as well as two stones in contralateral kidney

acid excretion was 400 mg /24 hours which increased to 990 mg /24 hours on the drug

Patient A H , with a lesion at D-7 and prior to surgery for renal calculi had two recurrent stones in the right kidney of 18 mm by 12 mm and 20 by 12 mm respectively, at the time therapy was started After eleven months of therapy the two stones showed little change, but two new stones appeared in the same kidney and grew to 8 mm and 4 mm in diameter The initial mean glucuronic acid excretion of 455 mg /24 hours increased to 975 mg /24 hours during treatment

Patient J G with a cervical lesion and no prior renal surgery, had a single 10 mm by 7 mm stone on the left side which grew to 15 mm by 15 mm and in addition, another 12 mm by 10 mm stone developed in the same kidney and two 13 mm by 7 mm stones in the contralateral kidney within the seven months of therapy The initial mean glucuronic acid excretion of 700 mg /24 hours increased to 1300 mg /24 hours while taking the drug (fig 3)

DISCUSSION

Chemical analysis of many stones from these patients has shown most of them to be mixtures of calcium phosphate (apatite) and magnesium ammonium phosphate No theoretical reason has been advanced to suggest that increasing the urinary glucuronide excretion would alter the rate of deposition of the magnesium ammonium phosphate However, if the suggestion is correct that glucuronides increase the solubility of calcium phosphate then the administration of aspirin or salicylamide, which increases urinary glucuronides should inhibit the further accretion of apatite upon existing stones and in addition prevent the formation of new stones since the nucleus of most stones is apatite That this did not result is evidenced by the continued growth and/or recurrence of calculi in 53 per cent of the patients in this study which is considerably higher than that observed in the same type of patient in previous studies Whether the therapy was responsible for the increased rate is not possible to say but it does appear that the drug is without merit in preventing new growth of calculi in this type of patient

Previous reports relating the value of increased glucuronide output to decreased stone formation have noted that on 2 gm /day of aspirin or salicylamide the output of glucuronides as determined at rather infrequent intervals increased two or three times Our determinations made weekly, disclosed marked fluctuations in output so that it became necessary to use mean values for comparison When this was done interesting excretion patterns emerged The mean pretreatment excretion of glucuronic acid appeared to be related to the presence or absence of calculi In patients without calculi most of the mean values were in the 200–400 mg 24 hour range with a maximum of 450 mg /24 hours while those with calculi excreted mean values between 410–1500 mg /24 hours with most over 450 mg /24 hours On the used drug dosage, the excretion of those without calculi increased threefold (2 5–3 7) but the excretion of those with calculi increased only twofold (1 7–2 2) moreover in two cases with rapidly growing calculi, the mean values of excretion before treatment of 1500 and 1300 mg 24 hours did not increase at all Since the highest mean glucuronide value obtained on therapy was 1600 mg /24 hours, the lack of response of these two cases is not surprising

The observation that glucuronic acid excretion is normally higher in patients with existing calculi refutes the theory of protection against calculi growth by increased glucuronide excretion

It is interesting to note that unfavorable results following acetylsalicylic acid therapy have been found in normal individuals with renal calculosis

SUMMARY

Fifteen spinal cord injury patients with a history of, or existing calculi, predominantly apatite-magnesium ammonium phosphate type, were placed on acetylsalicylic acid and salicylamide 2 gm /day for periods ranging from 3 to 11 months

The continual growth of existing calculi and the development of new calculi during therapy were greater than previously observed for the same type of patient without any treatment

The mean excretion of glucuronides by patients with existing calculi is normally higher than by patients without calculi which would seem to vitiate the concept of protection against calculi growth afforded by artificially raising glucuronide excretion levels

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CYSTIC DISEASE OF THE KIDNEY IN INFANTS

JOSEPH W HOOPER, JR

Cystic disease of the kidney in infants is an uncommon and serious condition with usually grave prognosis The etiology of cystic disease of the kidneys is obscure and there is no agreement on the mechanism of the end result [1-7] Potter points out that various types of cystic disease are probably explained not by one theory but by several There is general agreement that polycystic disease of adults and polycystic or multicystic disease of infants are related but probably not the same disease The reports of unilateral cystic disease by Meland and Braasch,[8] Schwartz,[9] Wakeley,[10] Goodyear and Beard,[11] Lih and Waud,[12] Ravitch and Sanford,[13] and Spence[14] establish this as a clinical entity The autopsy findings of Rall and Odel[15] in which 13 per cent of 46 cases were unilateral support unilateral cystic disease

Table 1 is a clinical classification of cystic disease of the kidney in infants and is based on a review of the literature Unilateral multicystic kidney is the same as unilateral polycystic kidney This is not to be confused with multilocular cystic kidney as described by Meland and Braasch[8] and recently reviewed by Boggs and Kimmelstiel [16] Both conditions are unilateral with a normal kidney on the opposite side Solitary renal cysts are rare in infants with prob-

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Read at annual meeting of Southeastern Section of American Urological Association, Atlanta Ga April 7–11, 1957 Not submitted for publication until October 18, 1957

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TABLE 1

1) Unilateral multicystic kidney
2) Multilocular cystic kidney
3) Solitary renal cyst
4) Bilateral multicystic kidney
5) Infantile polycystic kidney
6) Adult polycystic kidneys found in infancy
7) Calyceal cyst

ably not more than fifteen cases reported [17, 20] They are unilateral and the treatment is surgical

Bilateral multicystic kidneys is perhaps the largest clinical group and is the same group that Potter[1] classifies as the largest group of polycystic kidneys In this type both kidneys are composed of enlarged cysts varying from 1–4 cm in size and are found in stillborn infants or in infants dying shortly after birth

Microscopically these kidneys show the same picture as those of unilateral multicystic or unilateral polycystic disease Infantile polycystic kidney forms 12 per cent of the series from the Chicago Lying In Hospital [1] This type of polycystic kidney of infants is composed of multiple small cysts of a uniform size extending uniformly throughout the substance of both kidneys It is incompatible with life and death usually results in the first 3 to 4 months

Calyceal cyst or pyelogenic cyst in infants is rare and is that condition reviewed by Yow and Bunts [21] These authors concluded this is probably of developmental origin and only mention one case in infants [22]

Finally there is the adult polycystic type of kidney disease which is seldom demonstrated in infancy or childhood because of the absence of symptoms and this usually manifests itself later in life, usually in the third or fourth decade Braasch and Schacht[23] have pointed out this may be the result of decreased blood supply such as arteriosclerosis which is an integral part of the general aging process

In the past four years, seven cases of cystic disease in infants have come under observation and I would like to discuss these individually at this time

CASE REPORTS

Case 1 D E, a 5½-week-old premature baby, was admitted to the hospital because of failure to gain weight The birth weight was 3 pounds 13 ounces and the weight on admission was 4 pounds 3 ounces The child was two weeks premature There were no brothers or sisters and there was no known kidney disease in either parent The general appearance was that of a malnourished, poor hydrated white female child No masses were palpable The initial im-

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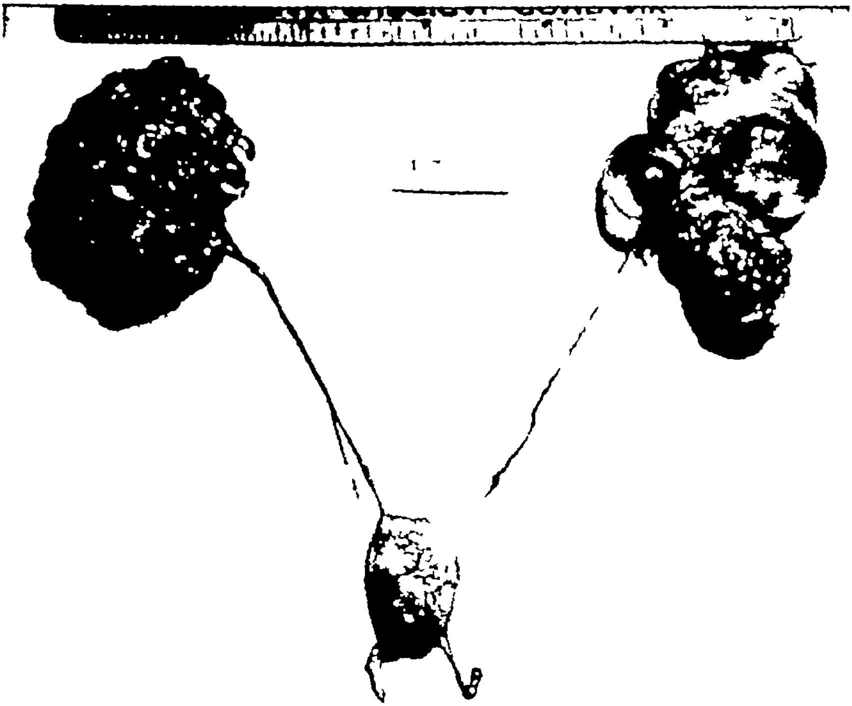

Fig 1 Both kidneys are displaced by multiple cysts with very little kidney tissue remaining

pression was that the child was a feeding problem with dehydration and emaciation The nonprotein nitrogen was 85 mg per cent and hemoglobin 13 6 gm The white blood count was 27,700 Cystoscopic examination was attempted two days following admission but was unsuccessful as the orifices could not be identified The child went rapidly downhill during the next two days and expired A postmortem examination demonstrated bilateral multicystic kidneys incompatible with life (fig 1) The patient also had cystic fibrosis of the pancreas A microscopic section showed much fibrous tissue and irregular size cysts

Case 2 J S a three-month-old child was admitted to the hospital with a diagnosis of pneumonia The patient was one of identical twins born six weeks prematurely One week prior to admission the patient had an apparent upper respiratory infection with resulting poor appetite and anorexia She had been taking fluids poorly for two weeks and had been vomiting intermittently for three weeks prior to admission There were no known familial diseases and the child was admitted to the hospital cyanotic and with gasping respirations In spite of penicillin and oxygen the patient died 12 hours after admission apparently of respiratory failure Laboratory examination prior to death revealed a hemoglobin of 10 gm and urinalysis showed 1 plus albumin and a few coarse granular casts The nonprotein nitrogen was 106 5 mg per cent An autopsy

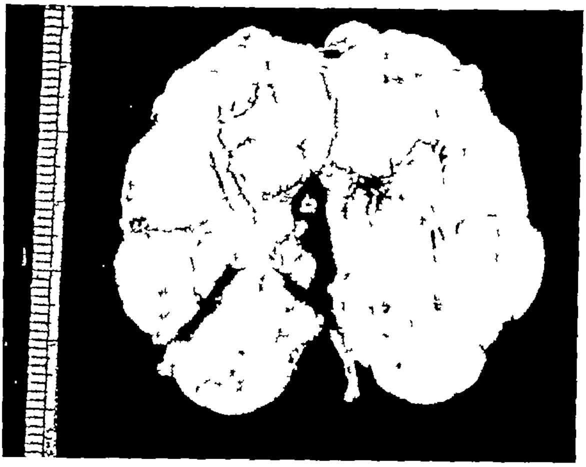

Fig 2 Cut surface of kidney reveals multiple tiny pinpoint cystic spaces measuring 1 to 2 mm in diameter These are uniform in size and occur throughout entire kidney substance

was obtained The only findings were enlarged bilateral lobulated kidneys weighing 89 gm The capsules were strongly attached to the cortex and on cut section the cortex could not be differentiated from the medulla Upon close gross examination the appearance was that of congenital polycystic kidneys (fig 2) The kidney substance was displaced by tiny pin point size cystic spaces measuring 1 to 2 mm in diameter No cystic disease of any other organ was demonstrated A section showed cysts of uniform size with very little fibrous tissue as compared with the first case presented

Case 3 D S, a three-month-old white girl, was the identical twin of the preceding patient and this patient died three days prior to her sister's admission to our hospital It was felt the cause of death was pneumonia, and an autopsy was obtained Dr J Howard Smith was kind enough to send us this patient's kidneys and the identical picture as seen in case 2 was found The kidneys weighed 91 4 gm and the microscopic sections were identical with those seen in case 2 Both cases 2 and 3 seemed to fall into the classification of congenital bilateral polycystic kidneys

Case 4 We are indebted to Drs Charles Graham and George Koseruba for the opportunity of including this case S P was a new born child who was seen at birth with a large mass filling the entire left side of the abdomen This child was a 7½ pound male born at full term uneventfully At birth the laboratory work revealed 17 2 gm hemoglobin, a white count of 16,550 with 44 lymphocytes, and 56 segmenters Urinalysis was negative for albumin, cells, or sugar An x-ray of the abdomen revealed the entire bowel shadow in the right half of the abdomen (fig 3) On physical examination a cystic mass was palpated extending from the costal margin down into the right pelvis This was felt to be the left kidney and was considered probably neoplastic At 3 weeks of age, the patient was explored through a left rectus incision and a large multicystic mass, filling the entire left side of the abdomen behind the mesentery and ex-

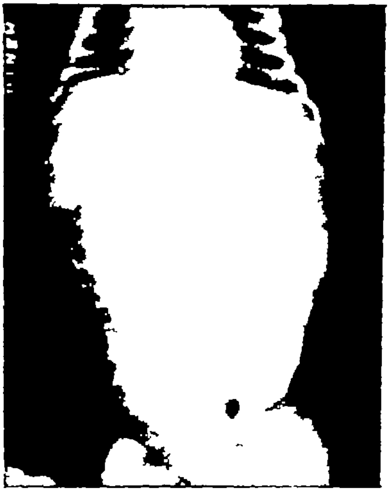

FIG 3 Flat film reveals entire bowel shadow to be in right side of abdomen with left side filled by a homogeneous mass

tending down into the pelvis was demonstrated This appeared to be the left kidney and the right kidney was normal to inspection and palpation The cystic mass was freed up easily and the ureter and the pedicle coming into the central portion were ligated and divided and the mass was removed. The specimen a large multicystic mass measuring 7 by 8 by 11½ cm , was composed of cystic structures measuring from 5 to 8 cm in diameter A microscopic section of this kidney showed irregular size cysts with much fibrous tissue between This was the same microscopic picture as seen in case 1 which was described as bilateral multicystic kidneys Postoperatively this patient did well and an intravenous pyelogram taken four years later showed a normal kidney on the left side with what we feel to be compensatory hypertrophy The child is gaining weight normally His urine is negative and his nonprotein nitrogen is 28 mg per cent

Case 5 G B a 1-year-old male child was admitted to the hospital for evaluation of a large mass in the right flank which had been present since birth This baby was born at full term uneventfully and at birth a mass was noted which was firm, nontender and extended from the right flank down to the level of the umbilicus An intravenous pyelogram showed good function on the left side but none on the right The parents were advised that the child should be followed closely and in the interim he was seen on five occasions at another hospital at which time intravenous pyelograms were made but no cystoscopic examination was carried out During the year prior to admission he had four episodes of pain in the right side with high fever and the mother believed that the mass had increased in size On admission physical examination was negative except for a cystic freely movable mass arising in the right flank extending anteriorly down to the region of the umbilicus The hemoglobin was 11 gm and the white count was 12 000 with 67 lymphocytes 27 polymorpho-

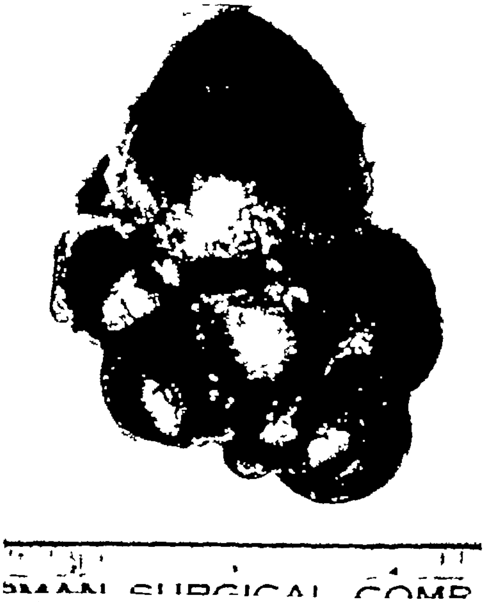

Fig 4 Unilateral multicystic kidney composed of various size cyst No functioning kidney tissue

nuclears and 6 eosinophils The urine was negative and concentrated to 10–24 The nonprotein nitrogen was 32 mg per cent Retrograde pyelograms were done on the right side and it was demonstrated that the dye went only to the level of L-2 Intravenous pyelograms were then performed and showed no function on the right side and excellent function of the left side with what I interpreted to be compensatory hypertrophy of the left kidney An exploration was done on the third day and a retroperitoneal cystic structure (fig 4) was removed from the region of the right kidney This was attached in the right flank by a vascular pedicle but no connection to the rudimentary ureter, which was identified in the lower part of the wound, was noted The patient had an uneventful convalescence and 8 months postoperatively is getting along well and his urine is negative The patient would seem to fall into the category of unilateral polycystic or multicystic disease, as would the previous case A microscopic section from this kidney is similar to the previous case and also to that found in bilateral multicystic kidneys

Case 6 This case is presented through the courtesy of Dr A I Dodson, Jr, of Richmond, Virginia A 3-month-old male child was seen by Dr Dodson because of bilateral flank masses causing no symptoms which were palpated on routine physical examination by the patient's pediatrician The nonprotein nitrogen was 28 mg per cent and the urine was negative The hemoglobin was 14 gm and the child was developing in a normal manner No family history was available An intravenous pyelogram taken at 4 minutes revealed a rather typical picture of bilateral polycystic kidneys (fig 5) We believe that this is the adult type of polycystic disease which is seldom seen in infants because it

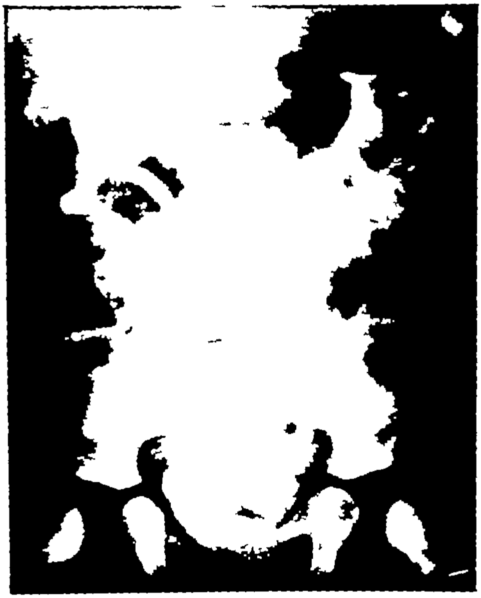

FIG 5 Five-minute intravenous pyelogram demonstrates enlarged kidneys bilaterally with deformity of both calyceal systems from multiple large cysts

causes no symptoms and is entirely compatible with life The only reason it was demonstrated in this child was due to the thorough physical examination by the pediatrician

The last patient is an example of a calyceal cyst of the kidney and is the second one of this type in infancy with which I am familiar[2] This patient was checked routinely at one year of age following plastic revision of the bladder neck in infancy because of fibrosis of the bladder neck Retrograde pyelography reveals a calyceal diverticulum, probably of congenital origin although the history of bladder neck obstruction might indicate that it was acquired as the result of

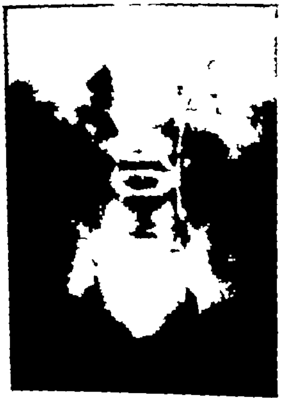

FIG 6 Large calyceal diverticulum is demonstrated at upper pole of left kidney

obstruction and infection (fig 6) This is producing no symptoms This patient will be re-evaluated from year to year and if the cyst causes symptoms then it will be resected

SUMMARY

The condition of cystic disease of the kidneys in infants is briefly reviewed A classification is set up from a clinical standpoint Two cases of unilateral multicystic or polycystic kidneys are presented and one case of bilateral multicystic kidney is presented Two cases of congenital type polycystic kidney are presented occurring in identical twins No other record is found of this in the literature and finally an unusual case of calyceal cyst of the kidney and a case of adult polycystic kidney in infants are demonstrated

CONCLUSION

Unilateral polycystic or multicystic kidney, large solitary renal cysts of infancy, and multilocular cyst of infancy should be treated by surgery Bilateral multicystic kidney and bilateral congenital polycystic kidneys are conditions found only too frequently in infancy and both of them are incompatible with life Adult polycystic kidney in infancy is recognized rarely and the treatment is merely supportive

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SIMULTANEOUS BILATERAL TRANSITIONAL CELL CARCINOMA OF THE URETER A CASE REPORT

VALENTIN GRACIA AND ELDON O BRADFIELD

Neoplasms of the ureter are seen infrequently, and the finding of this condition bilaterally could be considered a pathologic rarity Two cases have been reported in the English language literature In 1949, Ratliff, Baum, and Butler[1] reported a case of bilateral simultaneous primary carcinoma of the ureter, and in 1953, Felber[2] described an instance of asynchronous bilateral ureteral neoplasm A search of the English literature since 1953 has failed to disclose other instances, so it is believed that our report represents the third known case of bilateral carcinoma of the ureter, and the second case that has occurred simultaneously In the French literature in 1931 Chauvin and Cerati[3] mentioned two patients with bilateral tumors, but details are not available

CASE REPORT

A 44-year-old white oil-field worker was seen on February 16, 1955 The chief complaint was of blood in the urine Ten days previously, an episode of severe pain in the lower abdomen, nausea, and vomiting, followed by gross hematuria, had occurred He was hospitalized by his local physician, and within 48 hours, the nausea, vomiting, and pain subsided—but the hematuria persisted Attempted excretory urograms showed no excretion of the medium Cystoscopic studies were reported as showing bloody jets of urine from the right ureter and clear jets from the left Complete obstruction prevented passage of the ureteral catheters bilaterally Urological difficulty had not been evident prior to this episode, and throughout most of his life, this man had done extremely heavy labor About six months before being observed, however, he began having attacks of general malaise and slight fever which he attributed to the "flu " He had lost 25 pounds in weight In spite of this illness, he had passed a pre-employment physical examination five months previously

On admission, the blood pressure was 180 mm Hg systolic and 110 mm Hg diastolic, urinalysis showed red blood cells, grade 3, and blood urea was 114 mg per 100 ml Cystoscopic examination confirmed the presence of bilateral obstruction of the ureters at a level about 12 to 15 cm above the ureteral orifices

Bilateral nephrostomy drainage was established on February 19, 1955, but the area of obstruction was not explored The patient tolerated the procedure very well, but the first seven postoperative days could be described as "stormy " Nausea, vomiting, and a marked diuresis were present during this time His urinary output reached a maximum of 7,000 cc in one 24 hour period

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Accepted for publication October 3 1957

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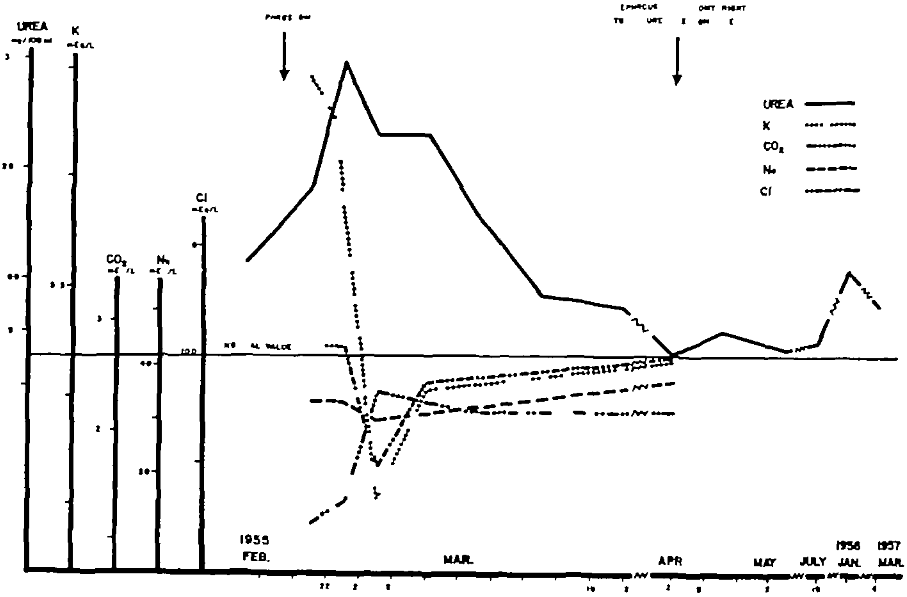

Fig 1 Electrolyte changes

Figure 1 illustrates the electrolyte changes during this and subsequent periods of hospitalization The blood urea rose rapidly to 300 mg per 100 ml After the seventh postoperative day, there was gradual but steady improvement The patient developed a good appetite, and was able to tolerate his diet well His renal function improved, and on his twenty-fourth postoperative day, the blood urea was 77 mg per 100 ml

At this time, retrograde and antegrade pyeloureterograms demonstrated a very small right kidney, a dilated upper right ureter containing several filling defects and obstruction of the ureter at the upper sacral margin The left pelviocaliceal system appeared normal in outline, but the ureter was dilated to the level of the upper margin of the sacrum See figure 2

The patient was dismissed from the hospital on March 16, 1955 He was ambulatory, but was advised to return in one month for re-evaluation of his condition

When he returned, he had gained some weight, some strength, and had developed a sense of well-being The blood urea was normal He had continued to pass large quantities of urine through the left nephrostomy tube, but nothing at all through the right Urographic studies were repeated, but no changes in the appearance of the ureteral defects were shown

On April 27, 1955, a Cherney-type incision was made, and the abdomen explored Intraluminal tumors were found in the lower thirds of both ureters, but there was no evidence of local or distant metastasis The right ureter was opened, and a typical transitional cell carcinoma was found The ureter was closed, and the region protected carefully against seeding The original abdominal incision then was extended upward to the tip of the right tenth rib The entire right ureter

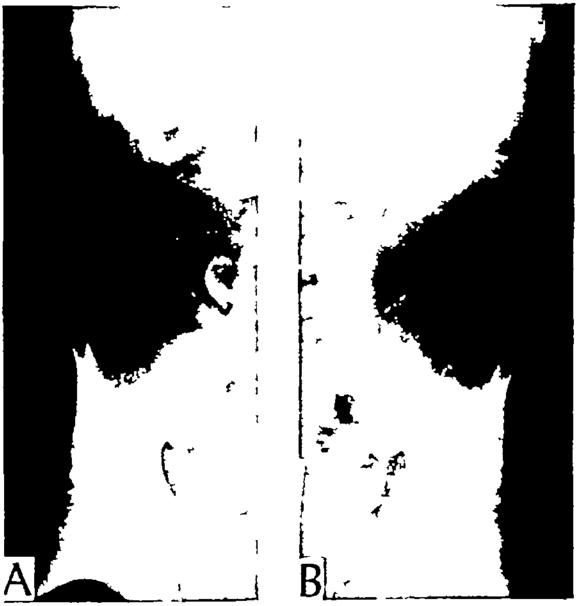

Fig 2 *A*, right retrograde ureterogram demonstrates filling defects *B*, left antegrade and retrograde ureterogram demonstrates obstructive and filling defect

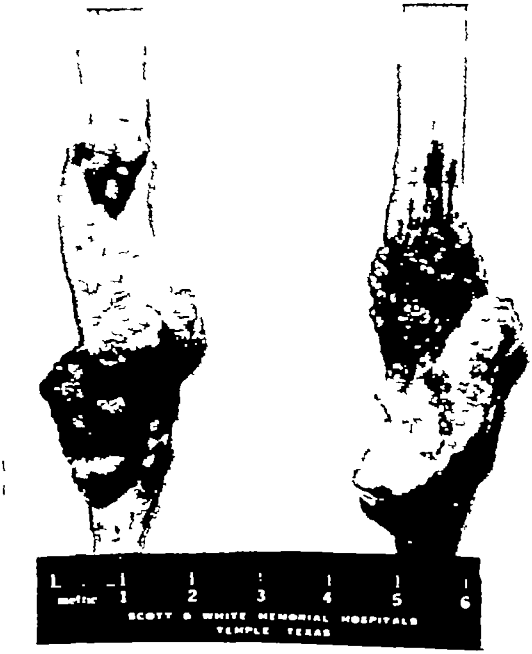

Fig 3 Photographs of short segments of each ureter showing tumors

and kidney were exposed, freed from surrounding tissue, and removed The left ureter then was exposed throughout its length At the upper end, dissection was carried to the ureteropelvic junction It was divided at this point, and the ureter removed A section of the bladder was removed with each ureter The previously established left nephrostomy was continued

Examination of the surgical specimens in the laboratory (fig 3) revealed three separate tumors almost occluding the lower one-third of each ureter All were transitional cell carcinomas, grade 2, with early infiltration into the muscle The largest tumor in each ureter measured about 4 by 0 5 by 0 5 cm The right kidney was atrophic and showed chronic pyelonephritis and glomerulonephritis

The postoperative course was uneventful, and the patient was dismissed from the hospital on the fifteenth postoperative day

Since dismissal, this man has progressed surprisingly well He has been observed periodically Repeated examinations of the bladder have failed to demonstrate the presence of an intravesical neoplasm The blood urea has not remained at normal levels, but has varied from 42 to 108 mg per 100 ml In the solitary left kidney, pyelonephritis has been controlled by the usual urinary antiseptics His appetite has been good, and his weight has remained stationary He does a moderate amount of work as a pool hall manager

DISCUSSION

In 1941, Felber treated his patient by performing a left nephro-ureterectomy, and eight years later, a right partial ureterectomy with fulguration of lesions To this, in 1951, he added partial cystectomy and partial colpectomy for recurrent lesions of the first operative site Ratliff, Baum, and Butler also kept continuity of the urinary tract after a left nephro-ureterectomy and a partial ureterectomy on on the right, followed by roentgen ray therapy

For our patient, a diagnosis of bilateral ureteral neoplasm was considered, but was not made preoperatively The existence of a retroperitoneal mass of a nonspecific nature was considered more likely

One may wonder why cystectomy was not performed as the patient now has a useless bladder At the time of operation, the added risk was not justified Also, by leaving the bladder, continuity of the urinary tract still could be re-established by using a segment of small bowel as a substitute for the left ureter The additional procedure will depend largely on the patient's progress, function of the remaining left kidney, and freedom from metastasis At present, the patient does not favor this additional operation Continued elevation of the blood urea, in spite of apparently adequate drainage by nephrostomy, indicates greater parenchymal damage to the remaining kidney than was estimated originally

SUMMARY

A case report concerning a patient with simultaneous bilateral transitional cell carcinoma, grade 2, of the ureter who has survived for over two years following right nephro-ureterectomy and left ureterectomy has been presented

Scott and White Clinic, Temple, Texas

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PRIMARY AMYLOIDOSIS OF THE URETER

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Amyloidosis of the genitourinary tract is relatively rare Several cases involving the bladder have been reported as well as one case involving both the renal pelvis and the ureter Since we have been unable to find any previous cases in the American literature involving only the ureter we believe that our case warrants reporting

CASE REPORT

A 12-year-old white girl had been well until December 1953, at which time she experienced pain in the right side of the abdomen and a normal appendix was removed During the next six months she experienced five episodes of pain usually starting in the right side of the abdomen but eventually involving the costovertebral angles and the left flank Gross hematuria accompanied these episodes Intravenous urograms, cystoscopy, and retrograde pyelograms elsewhere revealed some dilatation of the lower left ureter and left caliectasis The patient continued to have infrequent episodes of hematuria and pain until January 1955 at which time cystoscopy revealed edema about the left ureteral orifice with a blood clot protruding from the lumen

Physical examination revealed a healthy appearing patient Blood pressure was 110/60 pulse, respirations, and temperature were normal No significant abnormalities were found No tenderness was present in the flanks, abdomen, or in the costovertebral angles

The erythrocyte count was 3,850,000 and the leukocyte count 5,000 with an essentially normal differential count The urine was packed with red blood cells and showed many bacilli and a few leukocytes These bacilli did not react with acid-fast stains Bence-Jones protein determinations were negative Chest x-rays were within normal limits Intravenous pyelograms were inconclusive

Subsequently, cystoscopy was again performed and bloody urine was seen spurting from the left ureteral orifice There was no evidence of pathological process in the bladder and urine from the right ureter was clear Retrograde pyelograms showed an irregular narrowing of the lower third of the left ureter (fig 1) The tentative diagnosis was tuberculous ureteritis or neoplasm

Surgical exploration of this ureter was undertaken The lower third of the ureter was found to be dilated to approximately 1 cm and the wall of the ureter in this region was markedly thickened and showed what appeared to be a severe inflammatory process Biopsy taken from this area for frozen section examination revealed a chronic nonspecific inflammatory reaction with marked degenerative changes Due to the extent of these changes the possibility of further upward extension of the process and its uncertain etiology it was elected to

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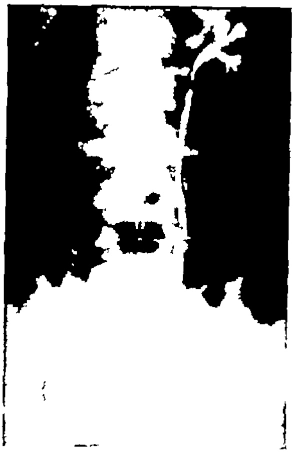

FIG 1 Lower third of left ureter, as seen by retrograde pyelography, shows irregular narrowing of lumen due to amyloid deposition in wall

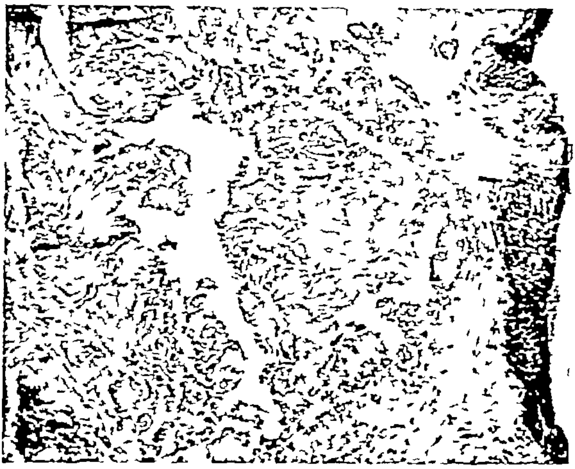

FIG 2 Section from involved area of ureteral wall shows marked degenerative process involving particularly submucosa This area gave red staining reaction typical of amyloid when stained with Congo red dye, and reddish violet response given by amyloid when stained with crystal violet Note mild hyperplasia and early ulceration of overlying mucosal surface

proceed with a left uretero-nephrectomy The patient's postoperative course was uneventful

The specimen received by the pathology department was a small, pale kidney weighing 60 gm with 15 cm of ureter attached The distal portion of the ureter was dilated and thickened, having a waxy, granular appearance, with patches of hemorrhage

Microscopic examination showed degenerative changes in the submucosa, muscle coats, serosa, and blood vessels, with old and recent hemorrhage and moderate lymphocytic response The mucosa showed areas of hyperplasia as well as ulceration Hematoxylin and eosin stains suggested a degenerative process as seen in amyloidosis Subsequent sections stained with Congo red dye as well as with crystal violet give the reactions characteristic of amyloid deposition The proximal portion of the ureter showed no changes and there was no involvement of the kidney or pelvis See figure 2

Two and one-half years later (August 1957) the parents reported that the child was in good health of normal weight for her age and free of genitourinary complaints

DISCUSSION

Amyloidosis is a process which may involve almost any tissue or organ and in which there is deposition of a homogeneous hyaline-like substance having characteristic staining reactions similar to those of starch Although the true chemical composition of this substance has not been established it is generally felt to be a complex protein

The condition occurs in several forms and is most simply classified as 1) primary amyloidosis or 2) secondary amyloidosis The primary form occurs in the absence of other disease is of obscure etiology and is rare It tends to be systemic and usually involves muscle and mesodermal tissues, although solitary deposits and tumors are not infrequent The secondary type is usually found following chronic suppurative conditions tuberculosis or multiple myeloma This type is most common and usually involves organs, particularly the liver and spleen

In view of the absence of a history of previous illness or chronic suppurative disease, the diffuse involvement of the lower ureter and the absence of clinical or laboratory evidence of multiple myeloma, this case must be classed as primary amyloidosis Not only is the unusual site involved in this case of interest, but also its occurrence at such a young age

SUMMARY

A case of primary amyloidosis of the ureter is described in a twelve-year-old girl The presenting complaints were pain in the costovertebral angle and hematuria

We wish to thank Drs Marion Coleman and Richard S Graves for furnishing the clinical history and Mr John Ford and Mr Reeder McKandles for their photographic work

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AN OPERATIVE TECHNIQUE FOR THE CORRECTION OF VESICOURETERAL REFLUX

VICTOR A POLITANO AND WYLAND F LEADBETTER

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In spite of accumulating clinical and experimental experience, the exact mechanism by which vesicoureteral reflux occurs is poorly understood Thus reflux and its correction still remains a major urologic problem Talbot and Bunts[1] in 1949 called attention to the importance of delayed cystography for purposes of demonstrating this condition

Several factors may produce or be responsible for the occurrence of vesicoureteral reflux Infection may result in scarring and fixation of the intramural ureter Certain congenital anomalies such as ectopic ureteral orifices, mal development of the trigone, decrease in obliquity or length of the intramural ureter as well as neurogenic disorders of the bladder or lower ureteral segment, may be responsible Reflux may develop secondary to vesical neck obstructions such as contractures, median bars, posterior urethral valves or strictures Trauma of the intramural ureter, incident to surgery of ureteroceles, meatotomies and transurethral resections, may be a causative factor

Prior to any attempted corrective surgery, the exact lesion or lesions responsible for vesicoureteral reflux must be determined and corrected when possible Excretory pyelograms, cystoscopy, panendoscopy, retrograde pyelograms and cystometric studies are done as indicated Determinations of residual urine are an important part of the workup Delayed cystograms or voiding cystourethrograms should be done on all patients with unexplained pyuria or residual urine This is especially true in children but applies as well to adults In addition, we consider the fluoroscopic observations of ureteral peristalsis of extreme importance Obviously the reimplantation of an atonic or adynamic ureter or segment of ureter will only lead to subsequent difficulties

The first step in the treatment of vesicoureteral reflux is elimination of the primary and/or contributing causes when possible We have seen reflux disappear with the elimination of infection We have seen it disappear or improve with the use of parasympathomimetic drugs, and we have seen it disappear with the correction of vesical neck obstructions The rapidity with which vesicoureteral reflux will disappear following correction of the primary cause will depend on the effectiveness with which the cause or causes were eliminated and on the degree of change that has taken place in the intramural ureter, in other words, whether the changes in the intramural ureter are reversible or not When reflux is not eliminated by such procedures, we feel that operative intervention directly on the ureter is indicated Our attention must be directed toward preventing irrevocable damage to the upper urinary tract The principle we have used is the

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Read at annual meeting of American Urological Association, Pittsburgh, Pa , May 6-9, 1957

[1] Talbot, H S and Bunts, R C Late renal changes in paraplegia Hydronephrosis due to vesicoureteral reflux J Urol , 61 870, 1949

creation of a submucosal tunnel As intravesical pressure increases, the submucosal ureter is compressed against the muscularis In addition, the submucosal ureter is elongated as the bladder distends In our hands this technique has been most effective in the correction of vesicoureteral reflux without producing obstruction to the upper urinary tract

THE OPERATIVE TECHNIQUE

The operative procedure on the lower ureteral segments is done entirely transvesically without mobilization of the bladder The ureteral orifices are identified and circumscribed, using a long handled scalpel A catheter in the ureter will help with dissection The incision around the orifice is carried through the mucosa and submucosa A traction suture is placed through the end of the ureter, and the intramural ureter is dissected free (fig 1, 4) Dissection of the retrovesical ureter is continued for a distance of 3–5 cm This is accomplished

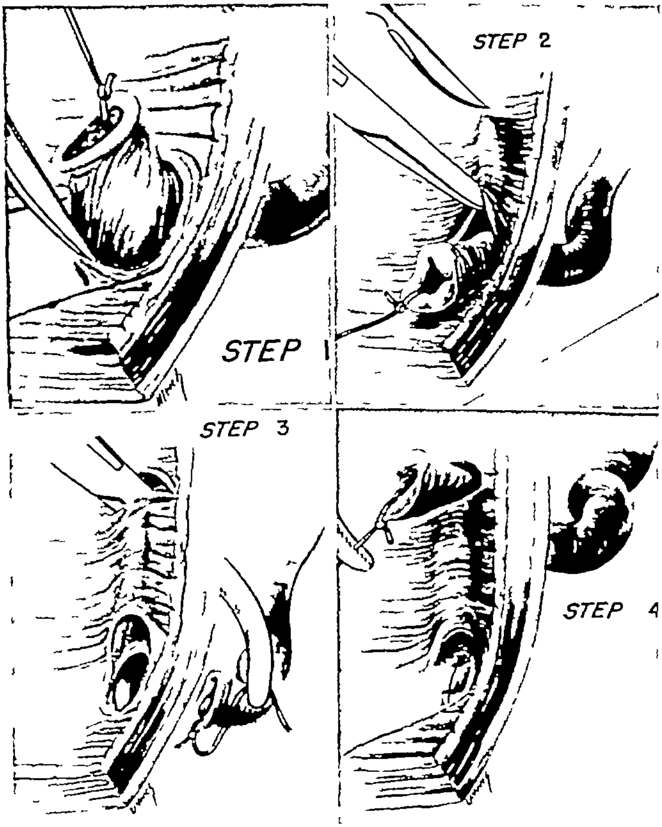


Fig 1 *Step 1* ureteral orifice is circumscribed and intramural ureter dissected free *Step 2* submucosal tunnel is made by gentle spreading of clamp beneath mucosa *Step 3* bladder is perforated Clamp is passed behind bladder grasping traction suture placed through ureter *Step 4* withdrawal of clamp pulls ureter into bladder at new site Original muscular defect is closed with interrupted sutures

by gentle traction on the intravesical ureter, dissecting the adventitial attachments from the ureter as they appear Care must be taken to stay in the adventitial layer and not strip or dissect the fibrous coat, which contains the vascular network, from the ureter The proper cleavage plane can easily be established by piercing the muscularis along the inferior margin of the ureteral orifice with a small clamp and gently spreading tissues This maneuver will usually open the proper plane for dissection Once a sufficient length of ureter has been mobilized, a submucosal tunnel of approximately two centimeters in length is made (fig 1, *B*) This is made in the approximate direction of the normal ureter, unless the position of the ureter and orifice is to be re-located The ureteral catheter, if used, is removed The mucosa is incised at the tip of the tunnel A clamp is forced through the muscularis of the bladder at this point, passed behind the bladder and allowed to enter the intramural opening The traction suture is grasped in the jaws of the clamp and the clamp withdrawn (fig 1, *C*) This maneuver pulls the ureter into the bladder at a higher level The muscular defect of the trigone is closed with a couple of interrupted fine chromic sutures (fig 1, *D*) The distal end of the ureter is carefully passed through the submucosal tunnel and sutured to the bladder mucosa, using four or five interrupted fine chromic sutures (fig 2) A small ureteral catheter is passed to the renal pelvis, the distal end is passed out the urethra A small balloon catheter is left indwelling through the urethra to drain the bladder, as well as anchor the ureteral catheters The bladder is carefully closed in layers No suprapubic catheters or drains are used The ureteral catheters, if draining well, are left in place for five or six days, otherwise, they are removed The urethral catheter is left for a week or so In all patients a moderate amount of hydronephrosis develops on removal of the ureteral catheters until the operative reaction and edema subside It is essential to keep the patient on appropriate antibiotic therapy during this period which usually lasts two to three weeks

We have used this procedure on seven patients The longest one has been

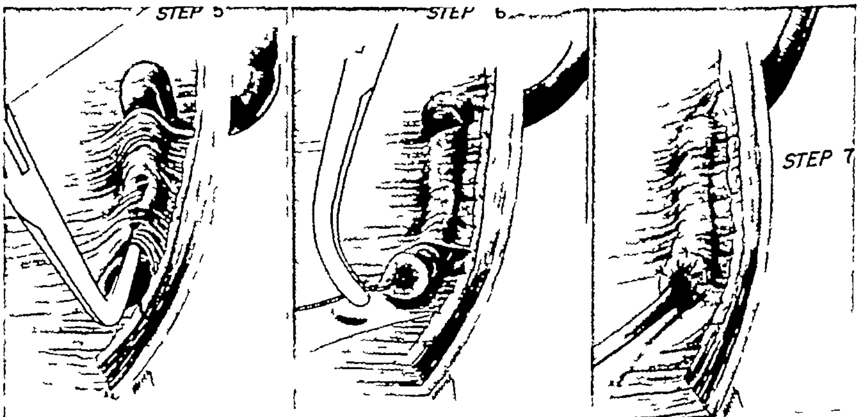


FIG 2 *Step 5* distal end of ureter is pulled through submucosal tunnel *Step 6*, ureter has been pulled through tunnel and is ready for mucosa to mucosa anastomosis *Step 7*, anastomosis completed by using several interrupted fine chromic sutures

observed for 20 months, the most recent, approximately two months The results to date have been most gratifying In each instance reflux has been eliminated The upper urinary tract has improved or shown no progressive changes All patients have remained essentially asymptomatic We realize that seven cases is not a large series, however, our results have been so uniformly good that this procedure, at least for the present, has solved a difficult urologic problem for us For purposes of brevity, four case reports are presented These are illustrative of the results obtained in the seven patients on whom this method of reimplantation has been used

CASE REPORTS

Case 1 S S, MGH No 863615 A 4-year-old white girl was admitted with a 5-month history of intermittent fever with temperature elevations to 105F occurring every 3–4 days She had mild irritative symptoms on voiding, consisting of burning and frequency Her fever was controlled with gantrisin, which she had been taking for six weeks prior to admission

On physical examination her temperature was 100 2F, pulse 90 respirations 25, and blood pressure 98/76 She was a small but otherwise normally developed child

Laboratory studies showed a hemoglobin of 12 6 gm and a white blood count of 11 000 The urinalysis revealed 20–25 white blood cells and 10 red blood cells per high powered field The nonprotein nitrogen was 34 mg per cent

Intravenous pyelograms (fig 3, *A*) showed slight hydronephrosis of a double left kidney with blunting of the calyces There was partial reduplication of the left ureter Cystogram (fig 3, *B*) demonstrated immediate ureteral reflux on the left

On cystoscopic examination the left ureteral orifice was found lateral to the trigone and sitting high on the left lateral bladder wall The right ureteral orifice was in its normal anatomical position The bladder outlet was considered normal

The diagnosis was ectopic ureteral insertion with ureteral reflux and pyelonephritis, left

Treatment consisted of reimplantation of the left ureter by creation of a submucosal tunnel This successfully corrected the vesicoureteral reflux (fig 3, *C*) Postoperative intravenous pyelograms showed good excretion from the left kidney without evidence of obstruction (fig 3 *D*) The child has remained asymptomatic for 20 months Microscopic examination of the urine is negative, and cultures have been sterile

Case 2 T B MGH No 863687 A 12-year-old white boy was referred because of bilateral hydroureters and hydronephrosis He had a two-year history of enuresis Eight months prior to his admission at the first hospital he had episodes of fever chills, nausea, and vomiting Right flank pain was often relieved by voiding Studies at that time revealed bilateral hydronephrosis A diagnosis of vesical neck obstruction was made and partial cystectomy and a Bradford Young procedure were performed The patient was kept on suprapubic catheter drainage over a long period of time to allow more adequate drainage of the upper

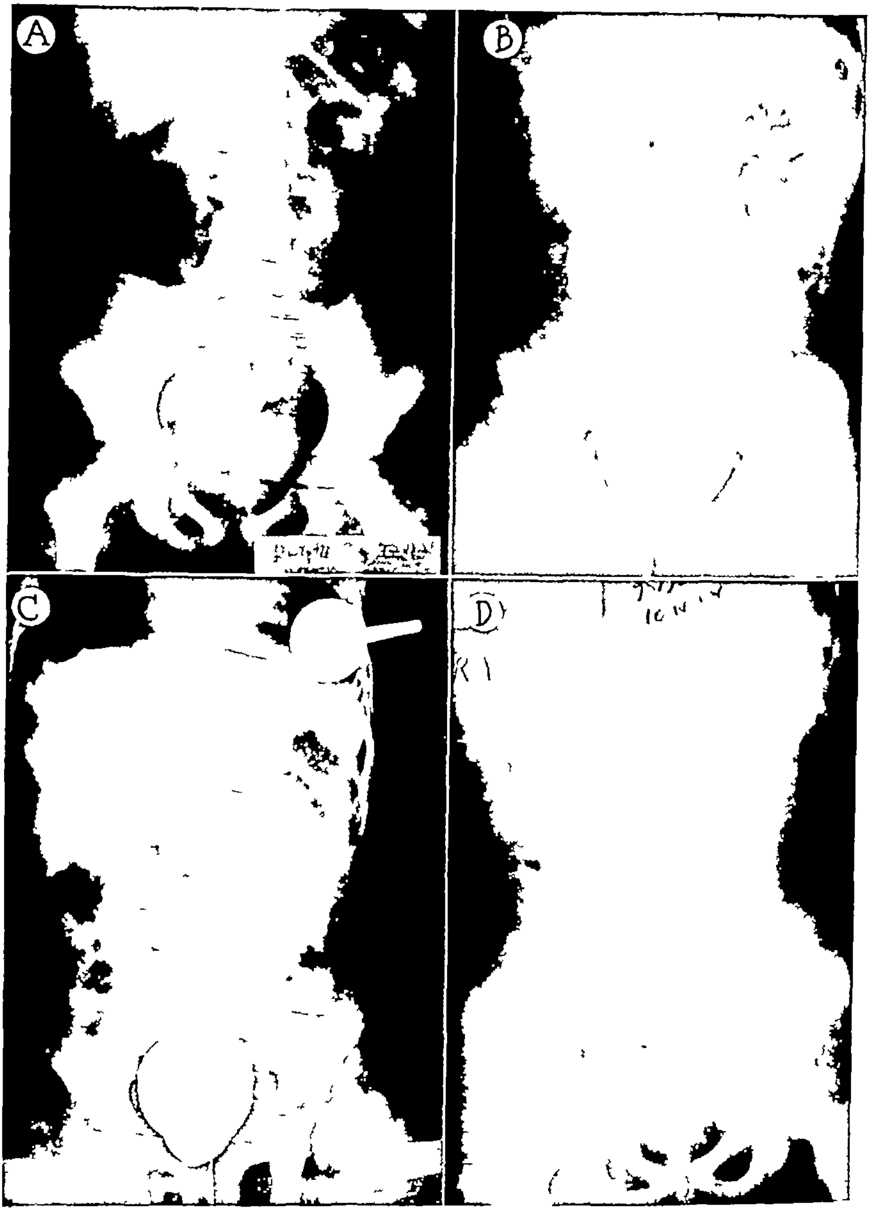


FIG 3 Case 1 *A*, preoperative intravenous pyelograms show blunting of calyces on left and bifid kidney and ureter *B*, preoperative cystogram, reflux, left Contrast medium in right pelvis represents continued excretion from intravenous pyelograms *C*, postoperative cystogram demonstrates absence of reflux *D*, postoperative intravenous pyelogram shows essentially same calyceal pattern as preoperative films

urinary tract On removal of the suprapubic catheter, his symptoms recurred The hydroureters and hydronephrosis became progressive On admission to our hospital he was found to carry residual urine between 150–200 cc A diagnosis of posterior urethral valves was made and these were resected This eliminated the residual urine and enuresis Because of the marked hydronephrosis and hydroureters, he was kept on catheter drainage for an additional five months

On physical examination his temperature was 98F, pulse 100 respirations 25 blood pressure 120/80 He was a well-nourished boy, but small for his age There was a well healed lower abdominal scar

Laboratory studies showed a hemoglobin of 15 6 gm and a white blood count of 11,800 His urine was loaded with white blood cells and an occasional red blood cell Urine cultures grew E coli and B proteus Nonprotein nitrogen was 24 mg per cent

Intravenous pyelograms (fig 4 A) demonstrated advanced bilateral hydronephrosis and hydroureters The sacrum and coccyx were displaced laterally to the right Cystograms (fig 4 *B*) disclosed immediate bilateral vesicoureteral reflux with dilatation of the ureters and calyces

Cystoscopy revealed a trabeculated bladder with chronic cystitis and inflammatory changes Vesical neck and prostatic urethra appeared normal

Cystometrograms were unsatisfactory because of the severe flank pain produced by free reflux on filling of the bladder

Preoperative diagnosis was bilateral vesicoureteral reflux It was strongly suspected that there was some neurogenic disturbance of the bladder as well

Treatment consisted of bilateral reimplantation of the ureters by a submucosal tunnel This was successful in correcting the vesicoureteral reflux (fig 4, *C*) Excretory urography (fig 4 *D*) revealed marked improvement of the pre-existing hydronephrosis and hydroureters During a year's observation the urine has contained from 6–8 white blood cells and, on occasions, has shown some bacilli, but the patient has had no further recurrences of fever and chills and the flank pain has been eliminated

Case 3 C W MGH No 947917 A 6-year-old white boy gave a history of recurrent fever and chills over a period of two years One year prior to admission he had several episodes of stomach "upsets" with cramps and difficulty in voiding Studies at another hospital revealed infected urine and left hydronephrosis A left nephrectomy was performed His symptoms persisted, and he was referred to this hospital for further evaluation and treatment

On physical examination his temperature was 99F, pulse 92, respirations 20, and blood pressure 120 60 He was a normally developed child There was a well-healed left flank scar

Laboratory studies revealed a hemoglobin of 12 8 gm and a white blood count of 10,000 Urinalysis showed 10–15 white blood cells per high powered field Urine cultures grew E coli Nonprotein nitrogen was 40 mg per cent

Intravenous pyelograms (fig 5 A) showed a left hydronephrotic double kidney prior to nephrectomy Intravenous pyelograms at this hospital showed a normal appearing right kidney with good function (fig 5, *B*) Voiding cystourethrograms

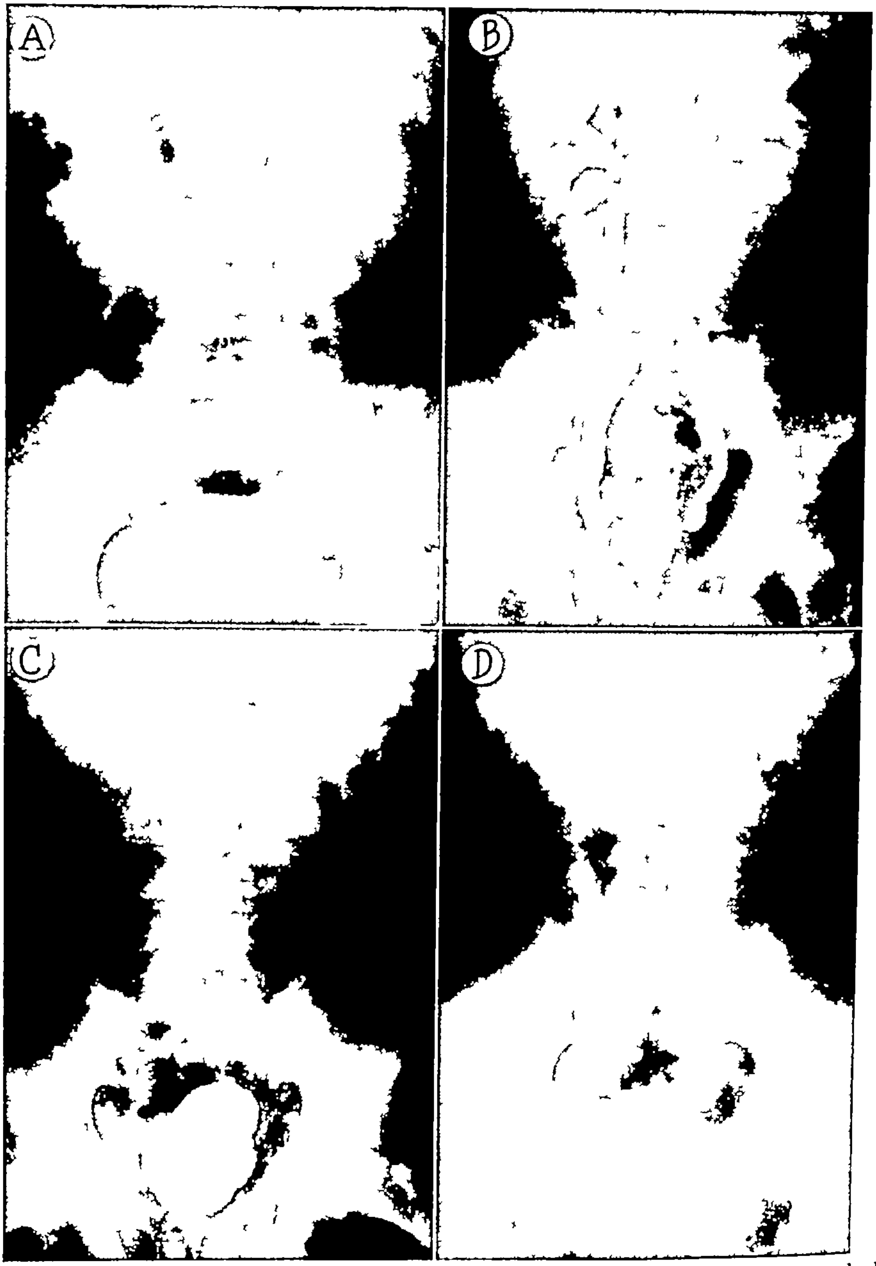


FIG 4 Case 2 A, preoperative intravenous pyelograms show delayed and diminished function and bilateral hydronephrosis and hydroureters *B*, preoperative cystogram exhibits immediate bilateral reflux with hydroureters and hydronephrosis Note bladder trabeculation *C*, postoperative cystogram Reflux has been corrected *D*, postoperative intravenous pyelograms show marked improvement of function and decrease of hydronephrosis and hydroureters

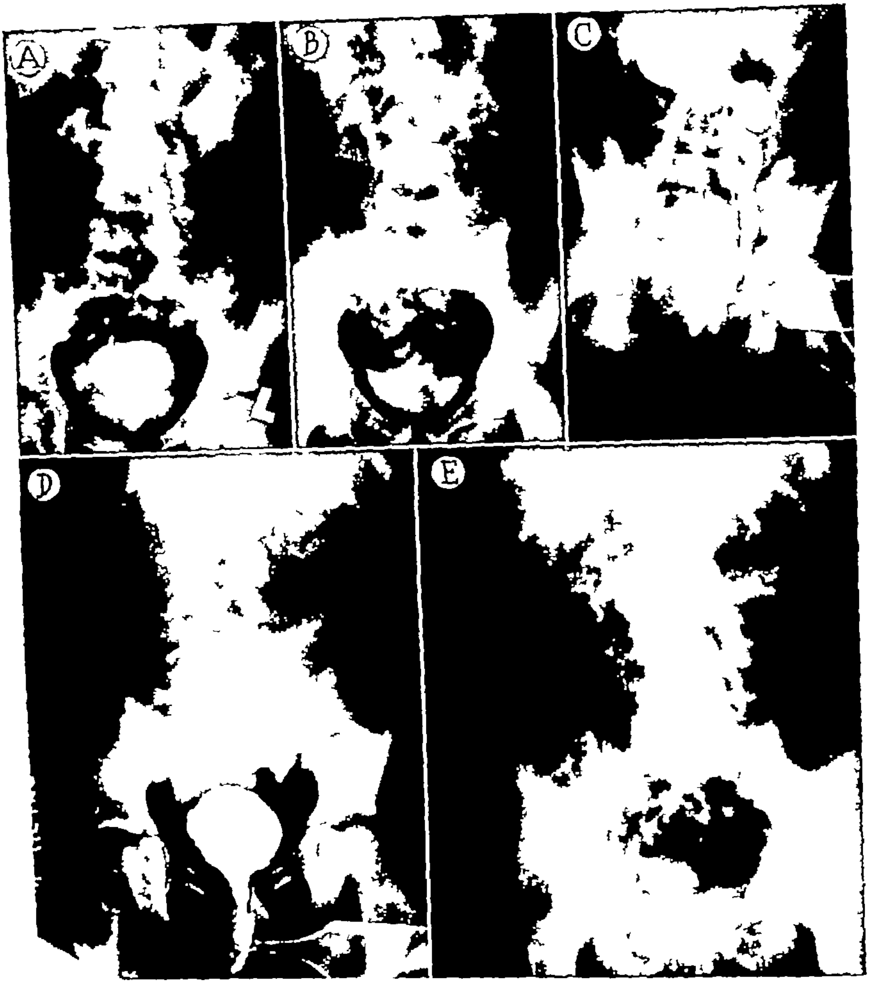


FIG 5 Case 3 *A*, intravenous pyelogram made prior to left nephrectomy shows double kidney on left and hydronephrosis of inferior portion *B*, intravenous pyelogram prior to reimplantation of right ureter shows normal pattern with good function Left kidney has been removed *C*, preoperative voiding cystourethrogram demonstrates extreme dilation of renal pelvis produced with voiding pressures in presence of reflux (Syringe is being used to deflect voided stream) *D*, postoperative voiding cystogram Reflux on right has been corrected Ureters on left were removed Note improvement in bladder outlet *E*, post reimplantation intravenous pyelogram Note absence of dilation in either calyces or ureter

(fig 5, *C*) demonstrated immediate reflux to the right kidney with marked distention of the renal pelvis and reduplication of the ureters on the left side

Cystoscopy revealed trabeculation of the bladder with early cellule formation and a moderate contracture of the vesical outlet with a small median bar

The preoperative diagnosis was contracture of the vesical neck with median bar formation, bilateral reflux, and reduplication of the left ureters

Operative treatment consisted of excision of the double ureters on the left, reimplantation of the right ureter through a submucosal tunnel, and a Bradford

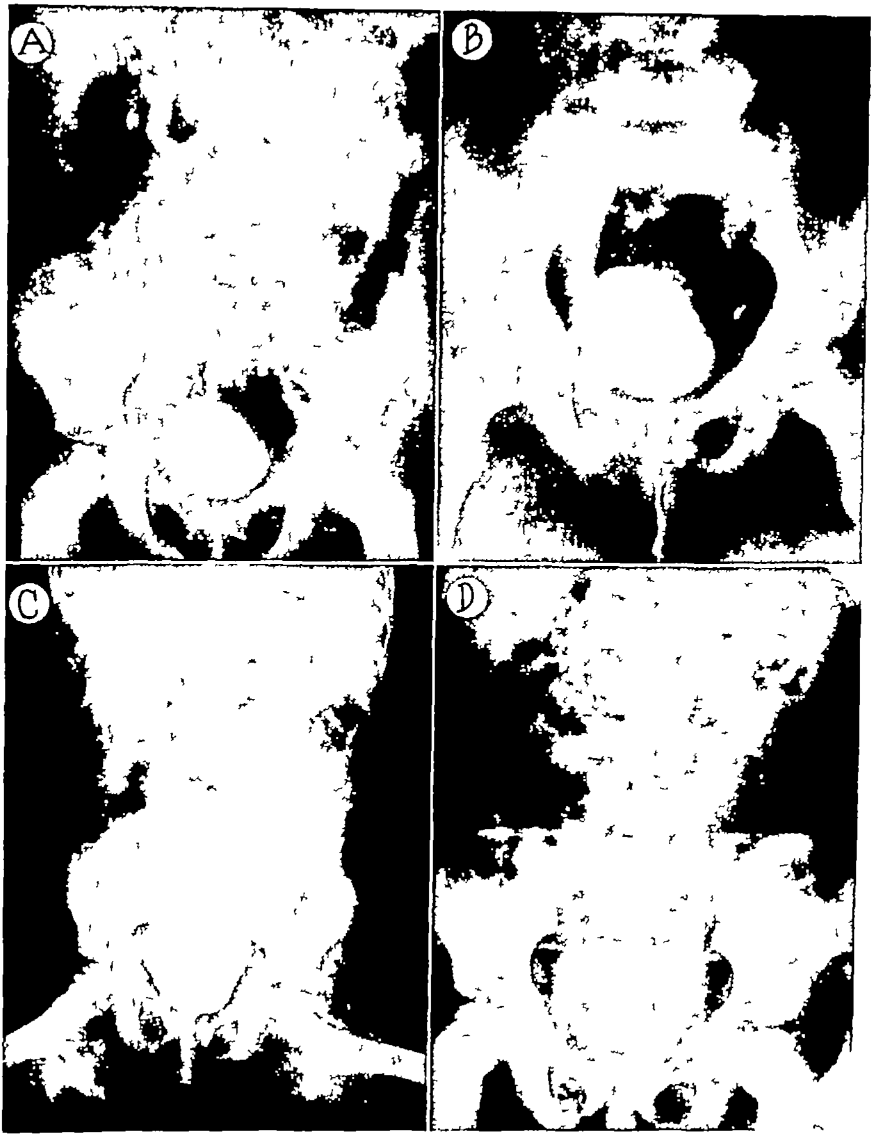


FIG 6 Case 4 *A*, preoperative cystogram demonstrates reflux on right *B*, preoperative voiding cystourethrogram demonstrates reflux up both ureters That on left side was missed preoperatively *C*, postoperative voiding cystourethrogram demonstrates reflux still present on unoperated left side Reflux corrected on operative side *D*, postoperative intravenous pyelograms show essentially normal excretion and collecting system

Young repair of the vesical outlet This succeeded in correcting the vesicoureteral reflux on the right side (fig 5, *D*) Postoperative intravenous pyelograms showed good function in the remaining kidney and a normal excretory pyelogram (fig 5, *E*) The urinalysis has remained negative Urine cultures have been sterile, and the patient has remained completely asymptomatic He has been observed over a period of six months

Case 4. J. F., MGH No. 836914. A 4-year-old white girl was admitted with a history of recurrent abdominal pains, frequency of urination, intermittent fever, and malaise of a year's duration. She had been treated intermittently for cystitis and pyelonephritis with chemotherapy and antibiotics. She had been checked on previous occasions for residual urine, and was found to carry approximately 10 cc. She was admitted with a three-day history of the above symptoms.

On physical examination her temperature was 104.5F, pulse 132, respirations 28, blood pressure 112/68. She was an acutely ill, dehydrated child with diffuse lower abdominal tenderness.

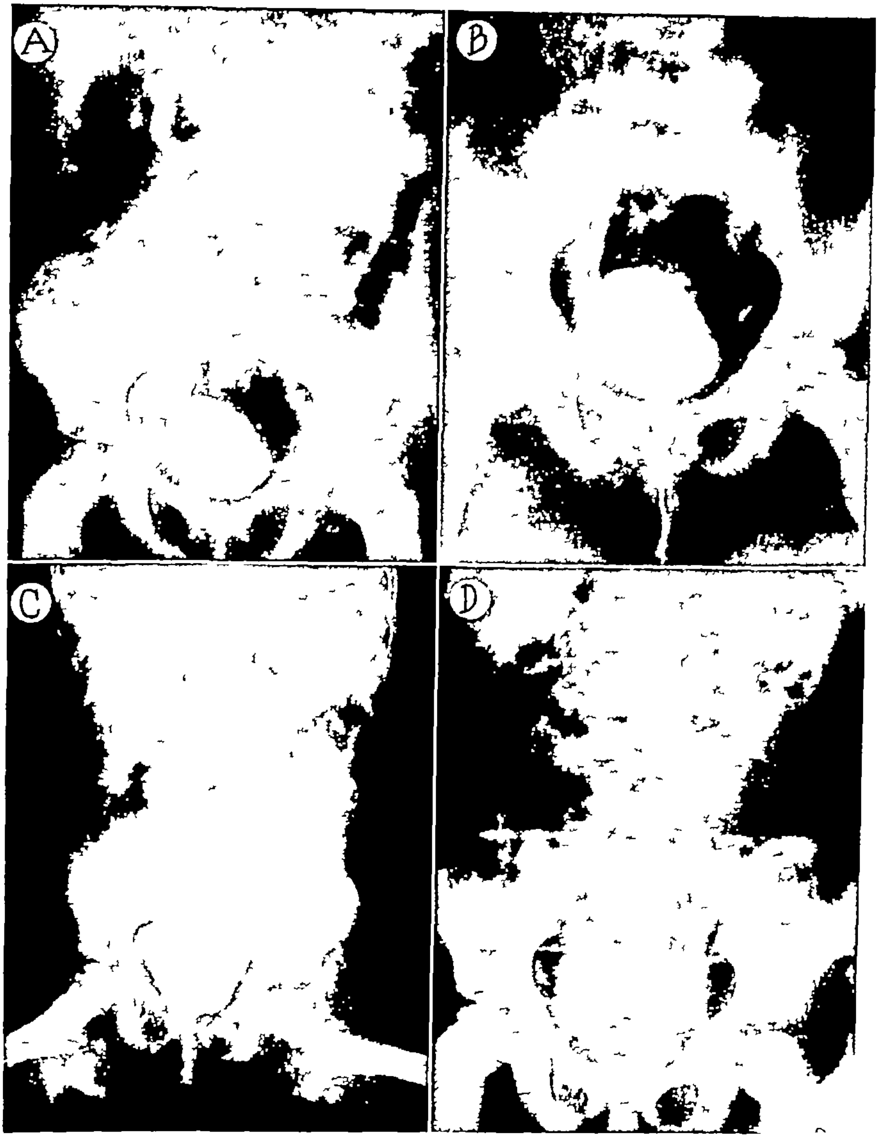
Laboratory studies showed hemoglobin of 10 gm. and a white blood count of 10,000. Urinalysis showed 35–40 white blood cells per high powered field and albumin 1 plus. Urine cultures grew coliform bacilli. Nonprotein nitrogen was 27 milligrams per cent. Intravenous pyelograms showed a normal upper urinary tract. A cystogram (fig. 6, *A*) showed reflux to the right kidney. A voiding cystourethrogram (fig. 6, *B*) again demonstrated reflux to the right, and on careful inspection reflux was visualized in the left lower ureter. This was missed preoperatively.

Cystometric studies revealed normal bladder function.

Preoperative diagnosis was ureterovesical reflux, right. Treatment consisted of reimplantation of the right ureter by a submucosal tunnel. This succeeded in correcting the reflux on the right, but reflux persisted on the left side (fig. 6, *C*). Postoperative intravenous pyelograms (fig. 6, *D*) demonstrated a normal upper urinary tract. The child has remained completely asymptomatic. Her urine has remained negative without medication.

ADDENDUM

Since the presentation of this paper in May 1957, an additional seven patients have undergone ureteral reimplantations, making a total of 11 cases and representing 21 ureteral reimplantations. In all instances vesicoureteral reflux was corrected. In all but one instance the upper urinary tract improved. In this one exception, the kidney was found to be nonfunctioning by intravenous pyelography, approximately 10 days postoperatively. The patient remained asymptomatic and afebrile in spite of the nonfunctioning kidney. Since we had not encountered this complication in previous reimplantations, the anastomosis was explored. The submucosal portion of the ureter appeared to be obstructed both by edema and some degree of stenosis of the reimplanted segment of the ureter. This portion of the ureter was resected and reimplanted. This represented the only complication in the remaining 21 reimplanted ureters.



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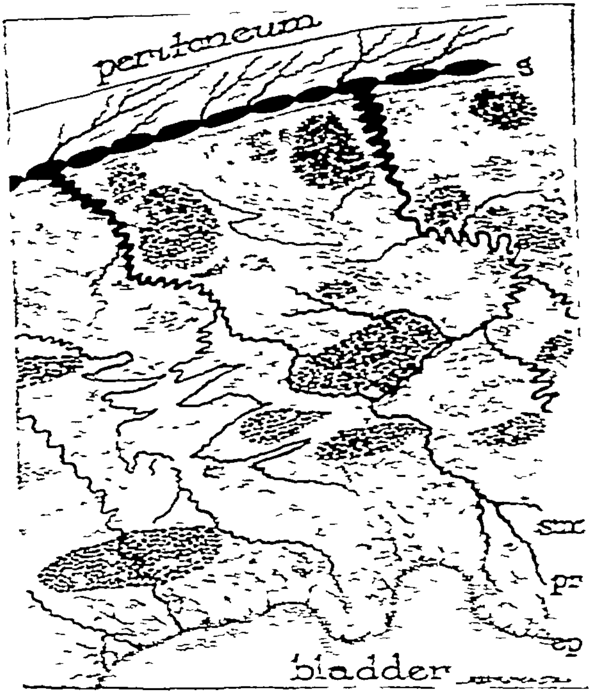

FIG. 1. Diagrammatic drawing of normal anterior bladder wall illustrates lymph vessels. Note tributaries coming from peritoneum on exterior surface and joining large valved collectors running in adventitia between peritoneum and bladder. Observe course of unvalved tributaries coming from submucosa and muscularis. These straighten out when bladder distends. From Powell

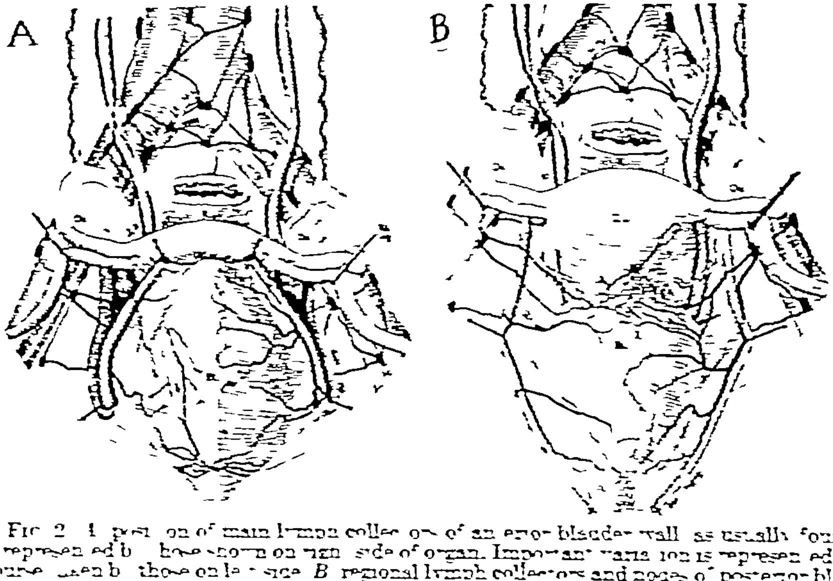

FIG. 2. A, position of main lymph collectors of anterior bladder wall as usually found is represented by those shown on right side of organ. Important variation is represented by course taken by those on left side. *B*, regional lymph collectors and nodes of posterior bladder. Note close relationship of main collectors with ureter, vaginal and hypogastric vessels as well as the ureter and cervix of uterus. From Powell

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THE ROLE OF THE LYMPHATICS IN INTERSTITIAL CYSTITIS (HUNNER'S ULCER)

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Interstitial cystitis was first described by Hunner in 1914 as a rare type of bladder ulcer in women Bumpus was the first to use the term, interstitial cystitis Many articles have been published but no uniformity of opinion exists regarding the etiology and treatment for this recurrent, resistant cystitis Most observers believe that infection and adjacent pelvic lesions have been etiologically cited but their removal has had little influence upon the course of the interstitial cystitis Kretschmer's 14 cases had no pelvic inflammatory disease Keene eradicated foci of infection in 25 women without appreciable relief of symptoms It has been suspected for a long time that an anatomic factor plays a part because the disease occurs mostly in women McDonald reported six cases in female children, aged 3 to 10 years

Every conceivable method of treatment has been tried for this disabling lesion, including removal of foci of infection, vesical distension, electrocoagulation of the ulcer, surgical excision, nerve section, oral, parenteral and topical medication None of these measures have proven routinely effective Hunner in 1915 reported that all of these rare bladder ulcers revealed a chronic granular urethritis Smith in 1952 reported that 20 (40 per cent) of his 49 interstitial cystitis patients had granular urethritis The urethritis was treated by endoscopic electrocoagulation

Powell made a 10 year study of the bladder wall lymphatics and their main collectors (figs 1 and 2) He was impressed by the similarity of Hunner's classical description of chronic inflammation, edematous thickening, increase in connective tissue and epithelial loss to the microscopic picture of ordinary progressive lymphatic edema Powell was searching for a specific factor responsible for the progressive bladder wall edema, anemia, fibrosis, trophic ulcer formation and bladder spasms due to the reflex nerve involvement He suggested a combination of predisposing etiological chronic infectious processes of 5 to 10 years' duration

The urethra and periurethral structures with their anomalies and poor drainage are a favorite site for chronic foci of infection The convergence and adequate drainage of the main bladder lymphatic channels, as demonstrated by Powell, could easily be influenced or prevented by a long standing urethritis, periurethritis or other adjacent infections

The object of this paper is to record and evaluate our results in the latest 11 consecutive patients with Hunner ulcer or interstitial cystitis After Hunner's ulcer was diagnosed the treatment consisted of mild electrocoagulation of the ulcer, biopsy if indicated, removal of all foci of infection (oral, pelvic, and urethral), and supportive measures, chemotherapy, cortisone and hormones

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Read at annual meeting of North Central Section of American Urological Association, Mackinac Island, August 29-31, 1957

Case No	Age	Status	Symptoms	Duration	Physical	Urine	Cystoscopy	Urethroscopy (Urethra)
1 I D	40	S	Freq , noc pelvic pressure diff voiding	3 months	Neg	2 4 WBC 10 20 RBC C Sterile	Ulcer Post fundal	Granular, skenitis
2 M B	32	M	Freq , noc	11 years	Neg , B P 200/115	0 2 WBC C Sterile	Ulcer (2) A P, trig mem	V N fibrosis, skenitis
3 B F	65	W	Freq , noc , pelvic pressure	4 years	Neg	0 2 WBC 0 2 RBC C Sterile	Ulcer Post fundal	Granular, V N pale, Skene's normal
4 M N	60	M	Freq , noc , abdominal pain	9 years	Neg	0 2 WBC 0 1 RBC C Menger Strep	Ulcer Post fundal	Urethral and V N fibrosis, skenitis
5 M T	44	M	Freq , noc , urgency, pain bladder & rt kidney, diff voiding	12 years	Neg	2 3 WBC 0 3 RBC C Menger Strep	Ulcer Fundal	Granular, skenitis
6 K T	40	M	Freq , noc , burning, abdominal pain	2 years	Neg	2 3 WBC 0 7 RBC C Sterile	Ulcer (connecting) A P fundal, trig mem	Granular, V N pale, skenitis
7 M N	40	M	Freq , noc , urgency, S & S Incont , rt kidney pain	3 years	Neg	0 1 WBC 1 8 RBC C Yeast	Ulcer Post fundal, trig hyperemic	Granular, V N pale, skenitis
8 A H	60	M	Freq , noc , urgency (burn), diff voiding	15 years	Neg	20 60 WBC 100 120 RBC C E coli	Ulcer post wall (secondarily infected) Biopsy inflam tissue	Granulocystic (biopsy trans carcinoma), skenitis
9 D K	43	M	Freq , noc , burning, pain (spasms)	9 years	Right bundle branch block	Occ WBC Occ RBC C Staph albus	Ulcer fundal	Granular skenitis
10 M O	48	M	Freq , noc , pelvic pressure, abdominal pain, bladder spasm	9 years	Neg , ulcers 9 mos after hyst'my	0 10 WBC 0 10 RBC C Sterile	Ulcers (2) post wall, trig mem	Urethral and V N fibrosis, skenitis
11 N S	68	S	Freq , noc , urgency, diff voiding	1 year	Neg , cystocele, urethrocele	10 15 WBC 8 10 RBC C Hem Strep	Ulcer anterior fundal	Urethra and V N fibrosis, skenitis

C culture, V N vesical neck, A P anteroposterior

SUMMARY OF CASES

The ages of these 11 patients ranged from 30 to 68 years, seven (63 5 per cent) were in their forties, two in the thirties and two in the sixties Eight were married, two were single, and one widowed Ten patients enjoyed good health (one with hypertension) while one had had a coronary attack followed by a bundle-branch block The bladder symptoms had been present from 3 months to 15 years, the average being 5 3 years All 11 patients had diuria and nocturia (three to eight times), four had urgency, two had burning, four had difficulty in voiding, three complained of pelvic pressure, three had suprapubic pain and five had urgency and/or stress incontinence See table 1

Eight patients had been treated elsewhere from 6 months to 15 years, two had been treated by urethral dilatation, three by office cystoscopy and electrocoagulation, two by hysterectomy for frequency of urination and one had had a partial transurethral resection Three were treated by the author, two, three, and ten years before for chronic urethritis, skeneitis, and meatal tumors

These 11 patients had careful general and urological examinations (table 2) Physical examinations were noncontributory except for the urethra The urethra was tender and/or thickened in all patients Ten had thickened palpable Skene's ducts Cystourethrocele on straining was present four times Preliminary excretory pyelograms were normal in eight and abnormal in three One patient had a right ureteropelvic stricture, one had a bilateral nephroptosis with right nephralgia, and one had bilateral ureteral duplication and urethral diverticula The pelvis was normal in six, five had had a hysterectomy (two total, three supracervical), 30, 7, 6, 2 years, and 9 months prior to the diagnosis of Hunner's ulcers The three cervical stumps revealed cervicitis One patient with a normal pelvis revealed chronic cervicitis

The urine was clear in ten patients and purulent in one Ten showed microscopic red blood cells and pus cells (0 to 10) per high power field One showed blood and pus, grade 3 The cultures of five urine specimens were sterile One showed only yeast, three showed meager growths of Streptococcus gamma, one hemolytic Staphylococcus albus, and one E coli The bladder tolerance varied from 100 to 400 cc (average of 315 cc) under caudal block anesthesia Bladder capacity readings were taken before the patients were anesthesized with intravenous sodium pentothal Four patients had residual urine of 15, 20, 30, and 110 cc respectively

CYSTOSCOPY AND URETHROSCOPY

Cystoscopy and urethroscopy under 30 cc of 1 per cent novocain caudal block anesthesia revealed the reduced bladder capacity (average of 315 cc), the membranous trigonitis in four cases, granular and/or cystic urethritis in 11 cases The vesical neck and deep urethra are interpreted as pale and fibrotic in four cases, and inflammatory, cystic, and/or granular in seven Skene's ducts were thickened in 10 cases and normal in one Four patients presented meatal papillomas

The location of the ulcers (determined with the aid of the air bubble) were as follows two in the fundus, four on the posterior fundal, one on the anterior hyperemic mucosal plaque bleeds on distension at 400 to 500 cc A well developed ulcer showed central blanching, radial arrangement of the mucosal vessels, and the mucosa tore at 250 to 350 cc distension A long standing ulcer lost some of its radial vascularity The margins became raised due to edema and fibrosis and the bladder capacity was markedly reduced Inactive ulcers were noted in four patients, 8, 6, 4, and 2 years after treatment In these four patients the persistent ulcers appeared less vascular with increased fibrosis in three Healing was slow In one patient the ulcer was small with intact mucous membrane which cracked at 375 cc distension

TREATMENT

In eight patients a transurethral resection was carried out at the time of the initial cystoscopy, the treatment included catheterization and incision of thickened Skene's ducts (seven cases) Three patients were originally treated for chronic urethritis and skeneitis and were resected later after the bladder ulcers developed Eight patients had one transurethral resection, two had two, and one had three Approximately two grams of tissue were removed from each patient, the least amount removed was one-half gram and the maximum was seven grams The bladder ulcers were mildly electrocoagulated once in five patients, twice in four, four times in one, and five times in one During the course of treatment two patients with single ulcers acquired double connecting ulcer while three patients had well developed connecting ulcers at the original examination When the treatment, including ulcer electrocoagulation was repeated, treatment of the residual granulations in the urethra was also carefully repeated The number of cystoscopic treatments ranged from one to six or an average of approximately three for each patient Long standing bladder ulcers seemed to require more cystoscopic treatments to stimulate healing

MICROSCOPIC SECTIONS

In 10 of the 11 patients, the tissue removed from the deep urethra and bladder neck was examined Microscopic sections revealed a striking similarity in these 10 patients They all showed dilated blood vessels, edema, fibrosis, lymphatic aggregates, and muscular hypertrophy (fig 3) Six showed metaplasia of the mucosa An early transitional carcinoma of the deep urethra was found once (fig 4) Endarteritis obliterans with focal calcification was noted in the patient who passed calculi three years after the original treatment for the bladder ulcer and a cystic urethritis The inactive fundal ulcer removed on August 12, 1957, by transperitoneal resection, revealed microscopically chronic proliferative inflammation of the urinary bladder (fig 5)

POSTOPERATIVE COMPLICATIONS

Few complications followed these treatments Two patients had postoperative hemorrhages at home during the second week which necessitated readmission into the hospital One was controlled with an indwelling catheter and the other by cystoscopy and electrocoagulation In one patient stress and strain inconti-

TABLE 2

Case No	X Ray	Previous Rx	Treatment	Result
1 E D	IVP—Normal	None	TUR—1951 Fulg ulcer (1x) Skene's incision	Asymptomatic 1957 No ulcer
2 M B	IVP—Normal	Urethral Rx—1941 Hysterectomy—1945 Cervix removed—1953	TUR—1951 Fulg ulcer (2x) & trig Skene's incision	Asymptomatic 200–500 cc No ulcer
3 B F	IVP—Normal	Oral medication	TUR—1954 Fulg ulcer (1x)	Minimal residuals
4 M N	IVP—Dupl ureters, urethral diverticula	Hysterectomy—1943 Urethral sounds 7 yrs	TUR—1950 Fulg ulcer (2x) Skene's incision	Residuals Urethral diverticula No ulcer
5 M T	IVP—Rt ureteropelvic stricture	Oral medication Cystoscopy Fulguration	TUR—1953 Fulg ulcer (1x) Skene's incision	Residuals due to contracted bladder No ulcer
6 K T	IVP—Normal	Uterine suspension Cystoscopy Fulguration	TUR—1952, 1954 & 1955 Fulg ulcer (5x) Skene's incision	Asymptomatic Voids 300 cc Ulcer inactive, removed surgically
7 M N	IVP—Rt nephroptosis	Oral medication Hysterectomy 1933	TUR—1953 Fulg ulcer (1x) Skene's incision	Minimal symptoms Estrogen controlled No ulcer
8 V H	IVP—Normal	Oral medication	TUR—1951 & 1955 Fulg ulcer (4x) Biopsy (2x) Skene's incision	Comfortable No Rx for 2 yrs Ulcer inactive
9 D K	IVP—Normal	Bladder tumor 1949 Hysterectomy 1952 ½ TUR 1954	TUR (½)—1955 Fulg ulcer (1x) Skene's incision	Comfortable Residual freq, noc No ulcer
10 M O	IVP—Normal	Urethral Rx—1947 Hysterectomy—1948	TUR—1955 Fulg ulcer (2x)	Comfortable Residual freq, noc Ulcer not healed
11 N S	IVP—Nephroptosis	Colon surgery—1948	TUR—1949 Fulg ulcer (2x)	Comfortable Residual freq, noc S & S Incont Ulcer inactive

fundal and one on the posterior wall In three patients two connecting ulcers were noted Two involved the anteroposterior fundal and one the posterior fundal wall

The diagnosis was made by filling the bladder visually following caudal block anesthesia The ulcers varied considerably in appearance In the early ulcer a

[illegible] Healing was slow [illegible]

[illegible]

[illegible] at the time of the [illegible] the treatment [illegible] and excision of these [illegible] Three patients were originally treated for [illegible] after the bladder ulcers [illegible] Eight patients had one transurethral resection [illegible] and one and three. Approximately [illegible] grams of tissue were removed from each patient [illegible] seven grams. The bladder [illegible] patients twice in four, four times in one and five times in one. During the course of treatment two patients [illegible] ulcer while three patients [illegible] original examination. When the [illegible] repeated treatment of the re[illegible] repeated. The number of [illegible] an average of approximately [illegible] seemed to require more [illegible]

MICROSCOPIC SECTIONS

In 19 [illegible] the tissue removed from the deep urethra and bladder was examined. Microscopic sections revealed a striking similarity in these 19 patients. They showed dilated blood vessels, edema, fibrosis, lymphatic aggregates and muscular hypertrophy (fig 3). Six showed metaplasia of the mucosa. [illegible] transitional carcinoma of the deep urethra was found once (fig 4). Endarteritis obliterans with focal calcification was noted in the patient who passed calculi three years after the original treatment for the bladder ulcer and [illegible] urethritis. The inactive fundal ulcer removed on August 12, 1957, on transperitoneal resection revealed microscopically chronic proliferative inflammation of the urinary bladder (fig 5).

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2 M B	IVP—Normal	Urethral Rx—1941 Hysterectomy—1945 Cervix removed—1953	TUR—1951 Fulg ulcer (2x) & trig Skene's incision	Asymptomatic 200–500 cc No ulcer
3 B F	IVP—Normal	Oral medication	TUR—1954 Fulg ulcer (1x)	Minimal residuals
4 M N	IVP—Dupl ureters, urethral diverticula	Hysterectomy—1943 Urethral sounds 7 yrs	TUR—1950 Fulg ulcer (2x) Skene's incision	Residuals Urethral diverticula No ulcer
5 M T	IVP—Rt ureteropelvic stricture	Oral medication Cystoscopy Fulguration	TUR—1953 Fulg ulcer (1x) Skene's incision	Residuals due to contracted bladder No ulcer
6 K T	IVP—Normal	Uterine suspension Cystoscopy Fulguration	TUR—1952, 1954 & 1955 Fulg ulcer (5x) Skene's incision	Asymptomatic Voids 300 cc Ulcer inactive, removed surgically
7 M N	IVP—Rt nephroptosis	Oral medication Hysterectomy 1933	TUR—1953 Fulg ulcer (1x) Skene's incision	Minimal symptoms Estrogen controlled No ulcer
8 V H	IVP—Normal	Oral medication	TUR—1951 & 1955 Fulg ulcer (4x) Biopsy (2x) Skene's incision	Comfortable No Rx for 2 yrs Ulcer inactive
9 D K	IVP—Normal	Bladder tumor 1949 Hysterectomy 1952 ½ TUR 1954	TUR(½)—1955 Fulg ulcer (1x) Skene's incision	Comfortable Residual freq , noc No ulcer
10 M O	IVP—Normal	Urethral Rx—1947 Hysterectomy—1948	TUR—1955 Fulg ulcer (2x)	Comfortable Residual freq noc Ulcer not healed
11 N S	IVP—Nephroptosis	Colon surgery—1948	TUR—1949 Fulg ulcer (2x)	Comfortable Residual freq , noc S & S Incont Ulcer inactive

fundal and one on the posterior wall In three patients two connecting ulcers were noted Two involved the anteroposterior fundal and one the posterior fundal wall

The diagnosis was made by filling the bladder visually following caudal block anesthesia The ulcers varied considerably in appearance In the early ulcer a

hyperemic mucosal plaque bleeds on distension at 400 to 500 cc A well developed ulcer showed central blanching, radial arrangement of the mucosal vessels, and the mucosa tore at 250 to 350 cc distension A long standing ulcer lost some of its radial vascularity The margins became raised due to edema and fibrosis and the bladder capacity was markedly reduced Inactive ulcers were noted in four patients, 8, 6, 4, and 2 years after treatment In these four patients the persistent ulcers appeared less vascular with increased fibrosis in three Healing was slow In one patient the ulcer was small with intact mucous membrane which cracked at 375 cc distension

TREATMENT

In eight patients a transurethral resection was carried out at the time of the initial cystoscopy, the treatment included catheterization and incision of thickened Skene's ducts (seven cases) Three patients were originally treated for chronic urethritis and skeneitis and were resected later after the bladder ulcers developed Eight patients had one transurethral resection, two had two, and one had three Approximately two grams of tissue were removed from each patient, the least amount removed was one-half gram and the maximum was seven grams The bladder ulcers were mildly electrocoagulated once in five patients, twice in four, four times in one, and five times in one During the course of treatment two patients with single ulcers acquired double connecting ulcer while three patients had well developed connecting ulcers at the original examination When the treatment, including ulcer electrocoagulation, was repeated, treatment of the residual granulations in the urethra was also carefully repeated The number of cystoscopic treatments ranged from one to six or an average of approximately three for each patient Long standing bladder ulcers seemed to require more cystoscopic treatments to stimulate healing

MICROSCOPIC SECTIONS

In 10 of the 11 patients, the tissue removed from the deep urethra and bladder neck was examined Microscopic sections revealed a striking similarity in these 10 patients They all showed dilated blood vessels, edema, fibrosis, lymphatic aggregates, and muscular hypertrophy (fig 3) Six showed metaplasia of the mucosa An early transitional carcinoma of the deep urethra was found once (fig 4) Endarteritis obliterans with focal calcification was noted in the patient who passed calculi three years after the original treatment for the bladder ulcer and a cystic urethritis The inactive fundal ulcer removed on August 12, 1957, by transperitoneal resection, revealed microscopically chronic proliferative inflammation of the urinary bladder (fig 5)

POSTOPERATIVE COMPLICATIONS

Few complications followed these treatments Two patients had postoperative hemorrhages at home during the second week which necessitated readmission into the hospital One was controlled with an indwelling catheter and the other by cystoscopy and electrocoagulation In one patient stress and strain inconti-

TABLE 2

Case No	X Ray	Previous Rx	Treatment	Result
1 E D	IVP—Normal	None	TUR—1951 Fulg ulcer (1x) Skene's incision	Asymptomatic 1957 No ulcer
2 M B	IVP—Normal	Urethral Rx—1941 Hysterectomy—1945 Cervix removed—1953	TUR—1951 Fulg ulcer (2x) & trig Skene's incision	Asymptomatic 200-500 cc No ulcer
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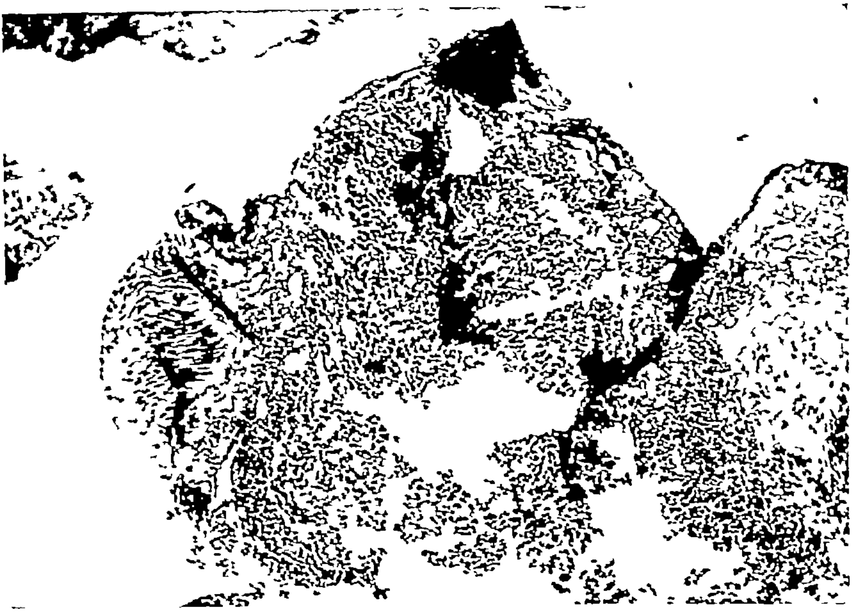

FIG 4 Early transitional cell carcinoma of deep urethra coexistent with severe granulocystic urethritis

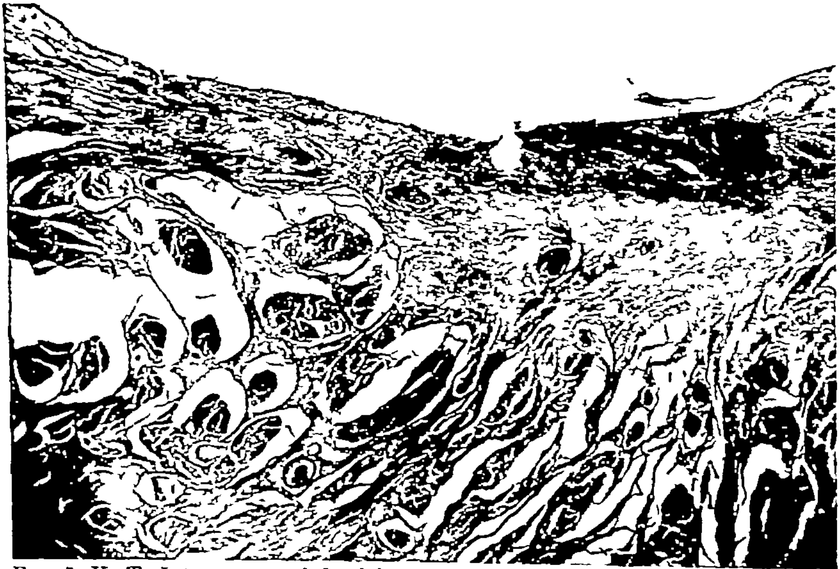

FIG 5 K T Intraperitoneal fundal resection of bladder ulcer shows inflammatory infiltration, submucous fibrosis, marked edema and hypertrophy of muscle

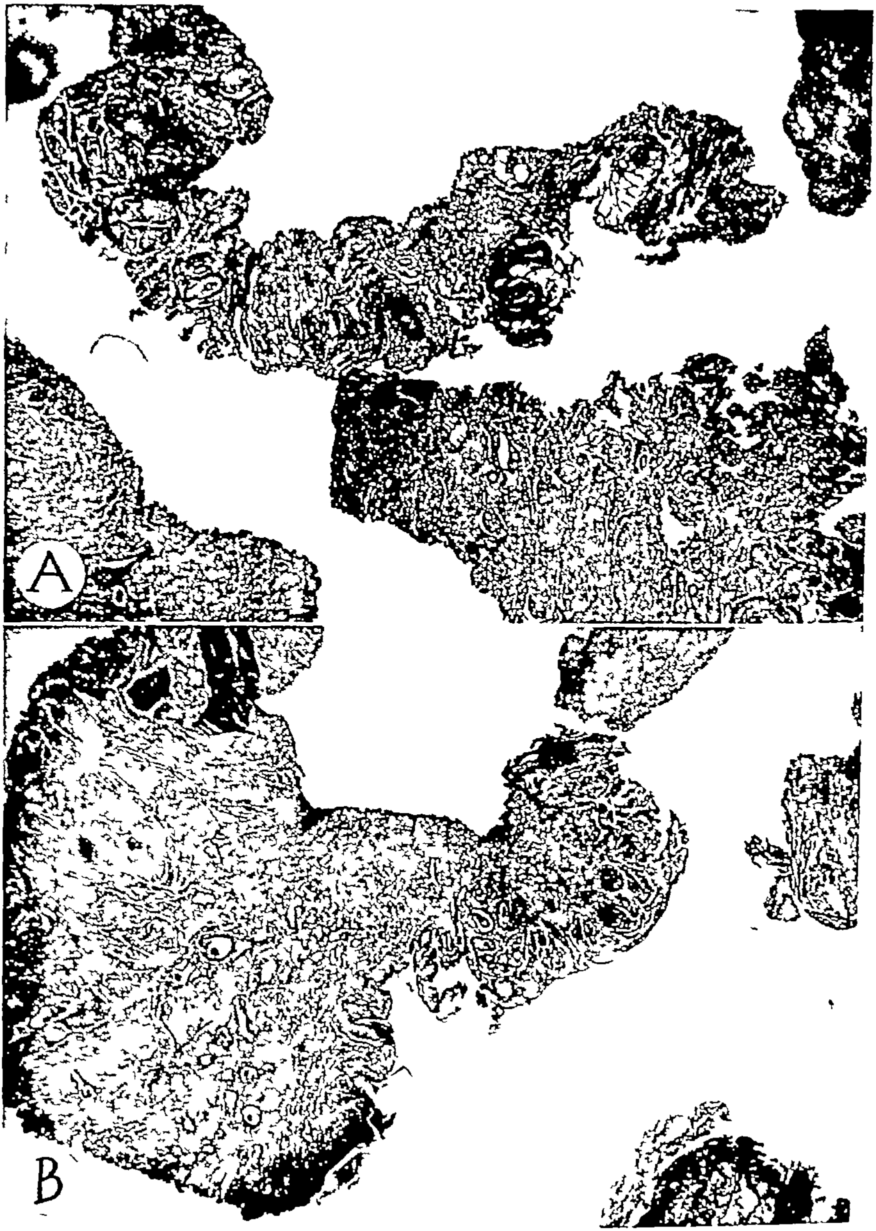

FIG 3 A, K T Hypertrophied muscle, chronic edema, minimal fibrosis and thickened vessels are present in tissue removed from deep urethra and vesical neck *B*, M O'B Bladder neck tissue shows submucous increased fibrosis, edema, dilated vessels, hyperemia and lymphocytic infiltration

nence developed and continued for six months Another acquired cystitis due to Proteus six months after the ulcer treatment, another, calcareous incrustation and calcification in the bladder ulcer three years after the original transurethral resection revealed an early transitional carcinoma of the deep urethra One

It is hoped that further investigation along this approach will be stimulated and lead to a better understanding of the etiology of Hunner ulcers

CONCLUSIONS

Eleven consecutive patients with Hunner ulcer were improved following eradication of all urethral foci, mild electrocoagulation of the ulcers and supportive measures

Powell's studies of the bladder lymphatics suggest that long standing urethritis can block the main bladder lymph channels and precipitate an ulcer in a few women

The eradication of all urethral foci is exceedingly difficult, repeated treatments are necessary for a maximum improvement in some cases

The recovery following treatment depends a great deal upon the type of ulcer found, viz , early, typical, or late advanced The advanced ulcers are resolved with repeated treatments but heal very slowly

Residual symptoms of frequency and nocturia persist due to bladder wall fibrosis and contracture

I wish to thank Dr Tracy O Powell of Los Angeles and Dr John W Huffman of Chicago for the use of their prints and slides

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patient, aged 30, acquired postoperative phlebitis of the lower extremities one month after discharge from the hospital Three patients revealed residual urethral granulations following the initial treatments Hospitalization for the patients having transurethral resection and ulcer electrocoagulation averaged 6 5 days No permanent injury such as fistulas or incontinence resulted from the operative treatment

FOLLOWUP STUDIES

In the followup it was noted that nine (81 per cent) of these 11 patients had been relieved of bladder pain for a period of 2 to 8 years, an average of 4 years Only frequency and nocturia (1, 2, or 3 times) remain due to fibrosis and reduced bladder tolerance In 10 patients, following treatment, cystoscopic examination was repeated In six (55 per cent) the ulcers were healed while in four the ulcers appeared inactive Two revealed double connecting ulcers with surrounding fibrosis and residual urethritis Cystoscopy has not been repeated in one improved patient and the ulcer status is unknown

Our classification of ulcers (early, typical, advanced, and inactive) coincides with Powell's research of the bladder lymphatics The longer the lymphatic obstruction, edema, and fibrosis have existed, the more devitalized the ulcer area becomes due to progressive edema and fibrosis resulting in loss of adequate blood supply Removal of urethral foci of infection seemingly altered the course of these bladder ulcers The treatment has reduced the usual recurrences, inactivated existing ulcers, and is followed by prompt or, in advanced lesions, by very slow healing Five patients responded favorably to one ulcer electrocoagulation and one transurethral resection, four responded satisfactorily to two ulcer treatments and one transurethral resection (one had a two-stage transurethral resection) One patient had four ulcer treatments and two transurethral resections, while another had five electrocoagulations and three transurethral resections It appears that long standing urethritis favors blockage of the fundal lymphatics and predisposes to ulcer formation in a few women Remote foci of infection, adjacent pelvic disease, or previous hysterectomy may not exert a direct influence upon the formation of a Hunner ulcer No specific bacteria are an exciting or precipitating factor

SUMMARY

This series of 11 consecutive patients is too small to warrant any complete analysis or opinion It does suggest, however, that adequate eradication of all infected urethral foci including trigonitis and skeneitis influences the course of interstitial cystitis or Hunner ulcers in women With extensive periurethral glands and anomalies, destruction of all infected urethral and bladder neck foci become exceedingly difficult In addition, the antibiotics, hormones, and cortisone therapy are helpful adjuncts in treatment The presently accepted treatment by vesical distension may at a later date be judged unnecessary and even harmful insofar as it adds trauma to an existing inflammatory lesion These 11 patients were not treated by overdistension of the bladder under anesthesia the surgical procedures needlessly performed on these Hunner ulcer cases where the true diagnosis has not been made The symptoms of his 223 patients caused them to be subjected to 264 operations without conflict On the authors' series, 54 major surgical procedures were performed needlessly

PATHOLOGY

Although the actual cause of interstitial cystitis is still unknown, certain factors of its pathology have been determined An excellent research by Powell showed blockage of lymphatics and/or blood supply in the dome of the female bladder which site is notoriously poor in collateral circulation Other suggested factors were pressure of the bladder against the symphysis pubis by the uterus and pelvic inflammatory disease

Hand summarizes the combined investigations of workers on the basis of infection, circulation, lymphatics, endocrine glands, nervous system, collagen diseases and allergy Sections through areas involved show thickening of the arterioles, dilatation of veins, and leukocytic infiltration about and within the nerves His conclusion was that the condition is initiated by a neurogenic factor Certainly more complete history-taking would assist in confirming this point

Carcinomatous changes in interstitial cystitis have now been reported in 17 instances Two cases each have been cited by Bumpus, Dixey, Hager, Howard, Rusche and Vose Hagner, Hand, Hunner, Kretschmer and the authors have each had one case This is not a great number in over 1000 cases of interstitial cystitis reported in the literature, but it does show that it occurs

Rupture of the bladder, obviously not publicized, in overdistending bladders, was found in 2 instances Eisenstaedt and McDougall had the scientific fortitude to report a case following the third fulguration We had one patient who survived such an experience elsewhere before she came to us

The ulcer, when seen, was most often located in the fundus near the air bubble, less often, lateral walls and floor There were 22 cases or 12 per cent of the total in which an ulcer was not seen In those cases in which the ulceration was present, 115 cases or 70 per cent of those observed were single, 50 cases or 30 per cent were multiple Of the multiple ulcerations 39 cases had 2, 9 cases had 3, and 2 cases had 4 ulcers

The bladder capacity was not stated in cubic centimeters in 23 cases Before therapy the average was 250 cc with a low of 30 cc and a high of 600 cc After therapy the average was 486 cc with a low of 60 cc and a high of 1110 cc for the entire series In the cases considered unimproved the average capacity before therapy was 132 cc and after therapy 258 cc

TREATMENT

The fact that new methods constantly are being tried to improve results in the management of interstitial cystitis proves that none are entirely satisfactory Partial cystectomy has been largely discarded as it has been shown that an ulcer will reappear on the unresected remaining portion of the bladder Complete cystectomy, although curative as far as the interstitial cystitis is concerned, is

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HUNNER ULCER OF THE BLADDER A REPORT OF 187 CASES

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The final solution to Hunner ulcer of the bladder has not been achieved, as voluminous literature concerning it will attest Yet each contribution offers some additional information, some further step toward its ultimate correction Fortunately, it is relatively infrequent in occurrence, rarely becoming malignant in character, but it has a suicidal potential in its severity and persistence Thus, to the individual patient afflicted, it is very real and a constant tormentor First mentioned by Mercier in 1836, it was not until 1914 that Guy Hunner described it so adequately that it has since borne his name Some fourteen other titles have been used by different authors to describe it but the actual process is best represented by the present accepted term of interstitial cystitis The etiology has yet to be established

MATERIAL AND CLINICAL DATA

The authors' series consists of 187 cases, all white, 176 or 94 per cent being female patients and 11 cases or 6 per cent males There are three other large series of interstitial cystitis previously reported which will be used for comparison In 1939, Kretschmer reported 138 cases with 119 or 84 per cent females to 19 or 16 per cent males In 1942, Higgins reported 100 cases with 94 females and 6 males In 1949, Hand reported 223 cases with 204 or 92 per cent females and 19 or 8 per cent males The youngest female in the authors' series was 14 (Hand 13) and the oldest female 78 (Hand 73) with an average female age of 50 years The youngest male in the present series was 21 (Hand 21) and the oldest male was 76 (Hand 60) with an average male age of 51 years The first case in this series was recognized in 1916 McDonald has reported interstitial cystitis in 6 children with ages ranging from 3 to 10 years Some 75 per cent of females were in the 40–69 year age group Unmarried females in this series were 44 or 25 per cent compared to 13 per cent in Hand's series

SYMPTOMS

The symptoms were those associated with small bladder capacity and/or irritability with superimposed infection Initial infection was present in 31 cases or 17 per cent One cannot make a diagnosis of interstitial cystitis where infection exists When it is not present, the primary qualifications are usually 1) a female patient, 2) small capacity, 3) sterile urine, 4) nocturia as well as diuria It would be helpful to remember that frequency without nocturia is usually functional while frequency with nocturia is usually organic In the authors' series, the duration of symptoms averaged a 4½ year interval from onset to diagnosis Some 23 cases or 12 per cent had had symptoms for 10 years or more Hand emphasizes

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TREATMENT

The fact that new methods constantly are being tried to improve results in the management of interstitial cystitis proves that none are entirely satisfactory Partial cystectomy has been largely discarded as it has been shown that an ulcer will reappear on the unresected remaining portion of the bladder Complete cystectomy, although curative as far as the interstitial cystitis is concerned, is considered rather radical and is rarely performed now even on very small bladders Nerve block and cordotomy have been tried but fail to be the methods of choice Injections endoscopically into the areas of ulceration of alcohol, hyaluronidase and cortisone have been recommended by other authorities Oral use of vitamin E, banthine and emetine hydrochloride have had their adherents X-ray has been tried unsuccessfully A new drug, chlorpactin, because of its success with small capacities produced by tuberculous cystitis, is being tried by many but the treatments are severe Initial reports are encouraging, but it is too early for final judgment Aniline dyes locally, and hormones on the basis of possible menopausal relationship have each been used without success

Our method of choice has been the time tested remedy of overdistention, silver nitrate instillation and fulguration in refractory cases After instilling 15 cc 5 per cent cocaine hydrochloride (4 per cent butyn for those sensitive to cocaine) into the bladder, it is left from 3 to 5 minutes This is followed by overdistention of the bladder with a 1 quart irrigator to absolute tolerance One may be certain that this has been done if the terminal few cubic centimeters on emptying are blood tinged This is followed by instillation of 2 per cent silver nitrate into the posterior urethra and vesical neck to which is added 30 cc 1/1000 silver nitrate and 90–120 cc of water This mixture is held for approximately 2 minutes, then thoroughly flushed out with sterile water Most patients are made more comfortable for their trip home if 5–10 cc additional local anesthetic is instilled into the bladder before removing the catheter The patient is cautioned to retain this for 10–15 minutes Fulguration is reserved for those patients whose progress becomes stationary or refractory This is a hospital procedure under general anesthesia with an electric cable current set at low intensity endoscopically Of the few patients who have been offered banthine in addition, approximately 50 per cent have noticed some improvement that we believe was due to the banthine alone

The average interval between treatments was found to be 42 days The loyalty of these patients is more for the relief they obtain from treatment than to the urologist Some 29 cases have been under observation for 1 month or less, 28 cases for 6 months, 19 for 1 year, 23 for 2 years, 9 for 3 years, 11 for 4 years, 8 for 5 years, 11 for 6 years, 8 for 7 years, 10 for 8 years, 8 for 9 years, 5 for 10 years, 4 for 12 years, 1 for 14 years, 1 for 15 years, 3 for 16 years, 1 for 18 years, 1 for 19 years, 2 for 22 years, 1 for 23, 24, 25, 28, and 36 years each Hospital fulgurations were required in 86 cases, 46 per cent The total number of hospital fulgurations was 140 At least twice this number of office fulgurations were performed under local anesthesia

TABLE 1 *Results*

Author	Cured or Greatly Improved	Improved	Unchanged	Total Cases
Kretschmer (1939)	20%	50%	30%	138
Higgins (1942)	17%	59%	24%	100
Hand (1949)	20%	50%	30%	223
Burford (1957)	14% (26)	79% (148)	7% (13)	187

RESULTS

The degree of improvement was judged by the patient's own testimony as the result of each treatment, the increased amount of bladder capacity and the amount of frequency and nocturia No deaths were due to interstitial cystitis, directly or indirectly Through the years, while under observation and/or treatment, a total of 8 patients died Three were cardiac deaths, 2 of these were 78-year-old men and one a 60-year-old woman Two patients, both women, aged 76 and 66 years, died from carcinoma of the bowel One woman aged 73 died of pneumonia and one aged 83 from a fractured hip One man, aged 48 years, died of carcinoma of the bladder

A composite tabulation containing comparative results of other series is shown in table 1

CONCLUSIONS

The precise etiology of interstitial cystitis is still unknown

A mode of identification and diagnosis is shown

A method of management of this problem is suggested

The results with 187 cases of interstitial cystitis are presented

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HEMANGIOMA OF THE BLADDER

DANIEL S LIANG

Hemangioma of the bladder is a true tumor In the literature on the topic it has been described under various names such as nevus, telangiectasia and cavernous hemangioma It is an unusual tumor in the bladder, and one that occurs in persons of either sex [1] As for age differential, the youngest recorded case was in a 27-month-old child and the oldest in a person 72 years old [2]

The tumor is congenital According to Herbut,[3] its increase in size results not only from an enlargement of the original vascular channels, but also from the budding and formation of new vessels which extends into the adjacent structures It is a slow growing tumor and this explains why symptoms may develop in later years Most of the lesion is in the region of the trigone

The lesion varies from the size of a pinpoint to one which could be described as massive or diffuse Superficially it is slightly elevated and sessile and appears to be bluish brown It bleeds easily The cut surface discloses fairly sharp demarcations but no encapsulation [3] Microscopically the tumor is surmounted by transitional epithelium The varix shows numerous large blood filled endothelial lined vascular spaces The tumor does not metastasize but it may spread to contiguous organs by direct extension Of the 41 cases reviewed by Segal and Fink[1] in 1942, only one became malignant When recurrence develops, it is probably due to incomplete removal of the tumor rather than to any malignant change

The most common symptomatology is hematuria and this usually with a long history of repeated attacks Other symptoms such as dysuria, frequency, and urgency, acute urinary retention or renal colic may be the only complaints

The treatment had been surgical in all the cases reported cystoscopic fulguration, transurethral resection, open surgery such as suprapubic fulguration, partial bladder resection, or cystectomy, depending on the size and location of the tumor Recurrences were noted by Segal and Fink in four cases of 22 cases treated Up to 1955, Graham and Bulkley[4] reported 46 cases of the tumor found in literature We were able to find since then cases reported by Fuqua, King and Ware,[5] Karris and Cammenos[6] and Ferulano[7] The two cases reported below bring the number to 51 to date

CASE REPORTS

Case 1 M S (169688), a white man, aged 52, was admitted to Roger Williams Hospital on November 10, 1956 complaining of severe right flank pain radiating

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[1] Segal, A D and Fink, H Cavernous hemangioma (report of case and review of literature) J Urol , 47 453–460, 1942

[2] Hyams, J A and Silberblatt, J M Hemangioma coincident with papillary carcinoma, case J Urol , 46 271–277, 1941

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to the right lower quadrant and nausea and vomiting of four days duration On admission the pain became a constant ache over the right costovertebral angle, with chills and temperature of 101F The patient had no hematuria dysuria frequency or urgency of urination He had had no bowel movements for two days Past history and family history were essentially negative Physical examination was negative except for tenderness over the right costovertebral angle Peristalsis was normal The prostate was grade 1 enlarged and smooth

Laboratory data Urine negative both chemically and microscopically Hemoglobin 13 7 gm. red blood cells 4 56 million white blood cells 11 000 blood urea nitrogen 20 mg per cent

Plain x-ray was essentially negative An intravenous urogram disclosed a faint outline of the pelvis calyces and upper ureter on the right side with marked hydronephrosis of the right kidney and dilatation of the upper portion of the right ureter Delayed films revealed a filling defect of the right side of the bladder

Cystoscopy and biopsy A sessile tumor bluish brown in color was seen on the right posterolateral wall of the bladder and the right half of the trigone involving the right ureteral orifice The orifice could not be located The rest of the bladder was essentially negative A moderate amount of bleeding occurred A biopsy obtained by a size 24 McCarthy resectoscope was surmounted partially by transitional epithelium partially by basophilic debris The underlying fibrous tissue was taken up by numerous large blood-filled endothelially lined vascular spaces The intervening trabeculae were occupied by acute and chronic inflammatory cells Impression Hemangioma (fig 2)

X-ray therapy was suggested and the patient was discharged three days later

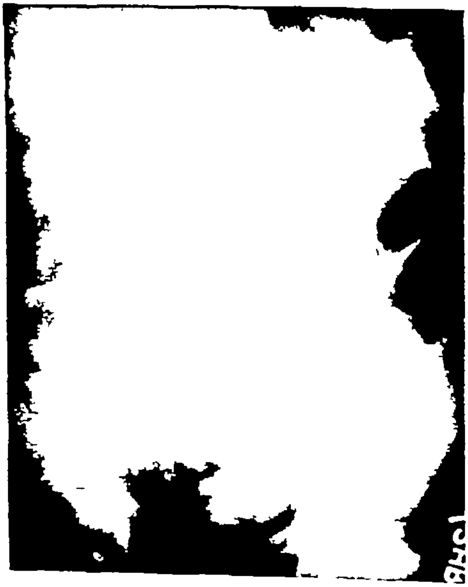

Fig 1

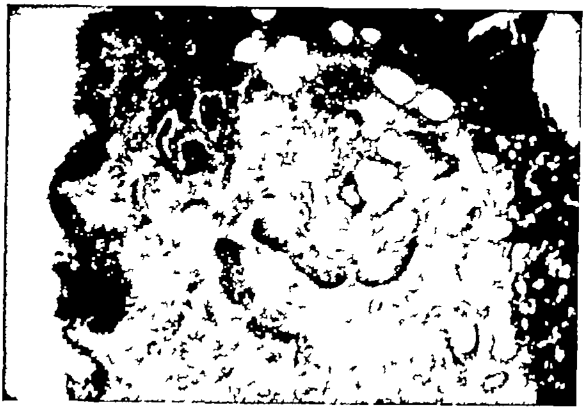

FIG 2

to be treated as an outpatient A total of 2500r-in-air H V L in 10 divided doses was given through the anterior port The back pain subsided on the third day after x-ray therapy The patient had been working since therapy started

On January 17, 1957 the patient was readmitted for observation and biopsy to see if the tumor had undergone any changes He had no complaint whatsoever

Cystoscopy revealed that the bladder was negative The right ureteral orifice was visualized and retrograde pyelography was negative (fig 3) Indigo carmine appeared in five minutes A biopsy obtained from the original site of the tumor showed transitional epithelium, submucosa and muscularis In the muscularis there was an area of fibrous tissue proliferation, possibly the result of therapy No evidence of malignancy was seen

Case 2 W B (2766), a white man aged 64, was admitted to St Joseph's Hospital February 1, 1957 complaining of gross blood and clots in the urine for two days The patient apparently had been well until two days prior to admission when he noticed bright red urine with clots, and dysuria He had no abdominal pain, nocturia, frequency, or urgency He had a similar attack two years ago and was told it was prostatitis He had no other symptoms His temperature was normal The past and family history was noncontributory

Physical examination was negative The prostate was slightly enlarged, smooth and soft, not tender, not fixed

Laboratory reports A culture of urine from the bladder yielded no growth Urinalysis albumin 3 plus, sugar negative, microscopically loaded with red blood cells White blood cells 5200, red blood cells 4 68 million, hemoglobin 13 9 gm , blood sugar 160, blood urea 15 mg per cent, CO_2 24 Electrocardiogram was normal Excretory urogram showed no evidence of renal disease Some irregularity was noted in the bladder shadow A Foley catheter was inserted on admission and the bleeding subsided over the weekend

Cystoscopy revealed minimal vesical neck obstruction A small bluish brown, broad base tumor, approximately 1 5 cm in diameter, was seen on the right side of the bladder above the ureteral orifice Moderate bleeding eventually stopped A biopsy was subsequently reported to consist of a tiny globular shaped, reddish brown tissue 2 mm in diameter Microscopic examination revealed a folded

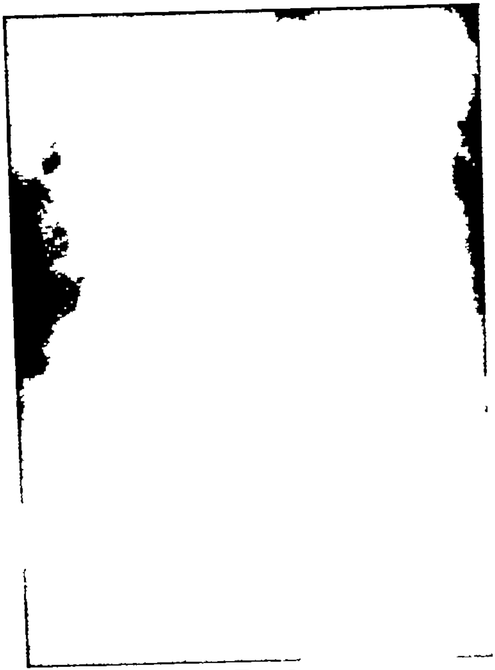

FIG 3

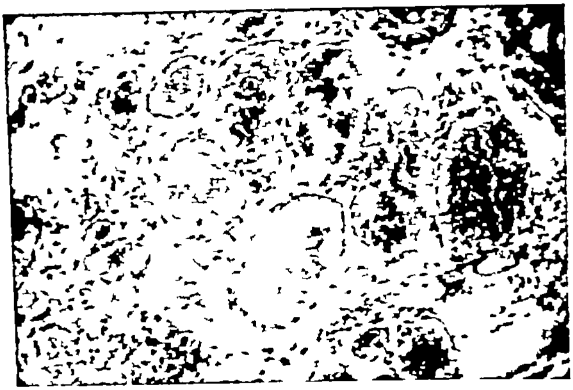

FIG 4

surface layer of stratified transitional squamous epithelium resting on an edematous connective tissue matrix The latter contained numerous dilated and engorged venous vessels and sinuses Diagnosis Hemangiomatous polyp of the bladder (fig 4)

The patient refused further treatment It was agreed that he would submit to the department of x-ray therapy as an outpatient, and see if the tumor would resolve

X-ray therapy 2500r-in-air, was given through the anterior port in ten divided doses There was no side effects The patient felt well Urine was clear

April 29 1957 cystoscopy was done in the office The bladder was normal in appearance throughout with slight reddening of the bladder mucosa The tumor had completely resolved No biopsy was taken

DISCUSSION

Both cases were treated by x-ray therapy, a method believed never before to have been used Excellent results were noted in both instances The first case report was interesting in that the patient had severe pain on the right side simulating renal colic The urine was negative I was surprised at the findings on intravenous urography and cystoscopy The tumor involved the whole right side and area of the trigone which proved to an hemangioma I contemplated doing either open fulguration or cystectomy, but observed that hemangioma of the spine, when treated with x-ray therapy, yielded good results [8] It occurred to me that the same therapy might be tried on a bladder tumor since it too was radiosensitive The dose planned was 2500r-in-air in divided doses in order to avoid skin reaction and cystitis Since the tumor was benign, I felt that radical surgery seemed drastic I reasoned that should the lesion not respond to x-ray therapy, surgery could then be contemplated The x-ray therapy proved successful, and no harmful side effects were noted Urine specimens were clear four months after treatment The post-irradiation biopsy in case 1, two months after therapy, was interesting in that the whole area appeared normal The second patient's tumor could easily have been amenable to transurethral resection and fulguration Because the patient refused further hospital stay but showed interest in x-ray therapy, he readily agreed to a trial treatment Cystoscopy two months later disclosed no tumor

Although post-irradiation cystitis can occur from 24 hours to six weeks or even as late as one year or more, neither patient has had any effect to date I believe from limited experience that a total dose of 2500r of x-ray therapy in air over the bladder will definitely resolve the hemangioma, and recommend that it be tried in massive cases before extensive surgery is contemplated In the smaller lesions transurethral resection and fulguration may be the wiser choice

SUMMARY

Two cases of hemangioma of the bladder have been added to a total of 51 cases reported to date

Experience in treating these tumors with x-ray therapy has been discussed It is concluded that massive cases should be treated with x-ray therapy before any extensive surgery is contemplated No complications due to irradiation occurred

Both patients are being checked periodically for recurrences and late irradiation side effects

I wish to make my sincere acknowledgement to Dr R R Hunt, radiologist at Roger Williams Hospital, whose kind help in devising the x-ray therapy for the cases presented has made this report possible

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[8] Thoms J and Fjeldborg, N Radiation treatment of hemangioma Acta radiol 40: 39–53 1953 (Also Yearbook of Radiology 1954–55, p 331)

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CARCINOMA OF BLADDER WITH CUTANEOUS RECURRENCE FOLLOWING PARTIAL CYSTECTOMY TEN YEAR CURE BY EXTERNAL IRRADIATION

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Advanced carcinoma of the bladder remains one of the most formidable therapeutic problems confronting the surgeon today Methods of handling this problem vary from radical complete cystectomy to internal or external irradiation and all combinations of the three

Internal radiation with needles or radon seeds gained early popularity and in some form or other has given probably more five-year cures than any other method of treatment Recent modification by Vermooten and other workers using cobalt beads offers promise The powerful betatron and supervoltage x-ray machines have proved disappointing External radiation has usually been reserved for palliation and even in that capacity has not been very effective This multiplicity of procedures is eloquent proof that no one method is completely satisfactory

The case to be presented was finally apparently cured by external irradiation alone, although surgery was employed as initial therapy A search of available literature suggests that this must be a rare outcome in far-advanced carcinoma of the bladder, which is the authors' reason for this presentation

CASE REPORT

A 60-year-old Portugese man was seen by one of us (C M B) on November 15, 1946, complaining of moderate urgency and gross hematuria of a few days' duration He had been under treatment at the Straub Clinic for diabetes for several years, but this was the first instance of hematuria A cystoscopy done in the office under sacral and local pontocaine anesthesia revealed in the dome of the bladder a sessile lesion which puckered the mucosa A tentative diagnosis of carcinoma was made and the patient admitted to The Queen's Hospital for preoperative stabilization of his diabetes On November 22, under spinal anesthesia, a suprapubic cystotomy revealed an infiltrating lesion in the dome which had penetrated all coats of the bladder and had extended through the vesical peritoneum

The location of the growth seemed favorable for excision A wide area of peritoneum and adjacent fat and alveolar tissues was removed including the dome and two-thirds of the bladder No attempt was made to radically remove lymph nodes, but great care was used to prevent implantation of the malignancy Closure with absorbable sutures was done without difficulty and a suprapubic urethral catheter furnished drainage

Pathologic examination was done by Dr Sumner Price of The Queen's Hospi-

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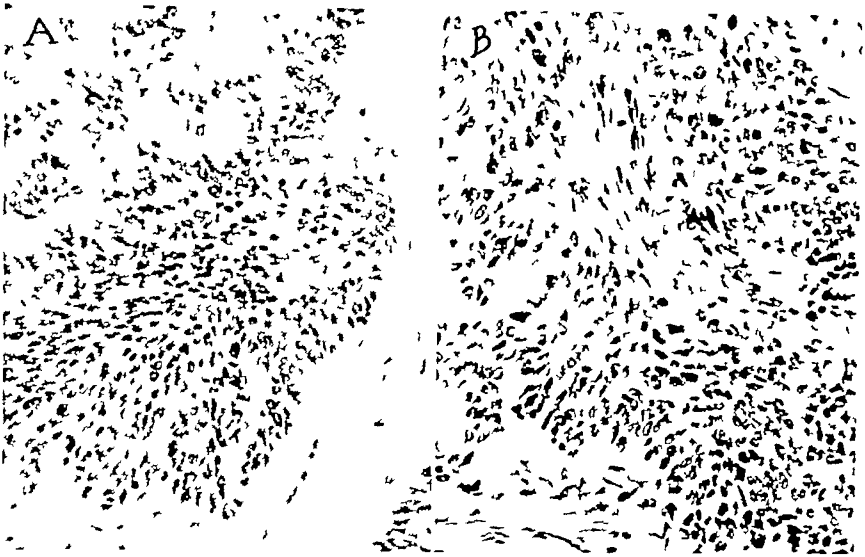

FIG 1 Photomicrographs *A*, Queen's Hospital slide No 12,624 shows fairly anaplastic (grade 2–3) carcinoma infiltrating bladder wall *B*, Queen's Hospital slide No 14,810 shows anaplastic carcinoma in abdominal wall Hematoxylin and eosin × 265

tal on five portions of tissue from the bladder, the largest measuring 5 by 5 by 4 cm Microscopic examination showed a fairly anaplastic carcinoma (grade 2–3) which had infiltrated the bladder wall extensively (fig 1, *A*)

Convalescence was uneventful until June 30, 1947, about seven months postoperatively, at which time a tender nodule 4 cm in diameter in the lower portion of the incision was noted The bladder capacity at that time was 4 5 ounces with nocturia about every hour but no dysuria A week later the mass was larger and less tender and a diagnosis of metastatic carcinoma was made A block dissection of the metastatic mass and surrounding tissue was done on July 15, 1947, again under spinal pontocaine anesthesia The tissue removed contained a 2 cm nodule of metastatic carcinoma which was identical, microscopically, with the original bladder carcinoma (fig 1, *B*) Again, convalescence was uneventful

On August 13, 1947, less than a month later, a second mass developed in the lower part of the abdominal incision It was believed that further surgery was not indicated, and the patient was turned over to Dr Phillip Arthur of Honolulu for deep x-ray therapy The prognosis was considered to be grave

The patient was treated on August 13, 1947, through October 15, 1947, inclusive He was given 2000r measured in air to four pelvic portals, namely, right and left anterior pelvic and right and left posterior pelvic The factors were 200 Kvp, 10 ma, 50 cm distance, 10 by 10 cm field, filter 1 mm cu and 1 mm Al, 200r (in air) daily

Much to our surprise, the patient continued to improve during the next 10 years Nocturia every hour without dysuria persisted but there were no other symptoms He regained his normal weight and vigor A cystoscopic examination in February 1950 showed no evidence of recurrence, and there was nothing in the chest or abdomen to indicate metastases

On March 18, 1957, a second postoperative cystoscopy by one of us (W S S) was again negative except for some trabeculation and moderate urinary obstruction by enlargement of the prostate, treatment of which was refused by the patient

The patient is now 71 years old, apparently in excellent health and free of metastases

DISCUSSION

This case represents an apparent 10-year cure of a grade 2–3 transitional cell carcinoma of the bladder Two attempts at local surgical excision of the lesion were done, and recurrence in the incision followed both attempts Palliative radiotherapy was then given without excision of the last recurrence, following which the neoplasm disappeared This unusual occurrence suggests that the tumor itself was exceptionally sensitive to radiation

The successful treatment of bladder carcinoma always has presented a great problem to urologists and surgeons alike, primarily because of the great variation in behavior that may be exhibited It is because of this factor that successful treatment may vary from superficial cystoscopic fulguration to total cystectomy with radical node dissection and ureteroenterostomy The use of roentgen therapy in its various methods of application, either alone or in conjunction with surgical excision, has materially improved the results of both open surgical removal and transurethral resection Interstitial or intracavity radiation with radium, radium emanations, or radioactive isotopes has proven to be superior to external therapy with the conventional apparatus

Rotational therapy employing supervoltage machines may prove to be an exception, however, and it may well be that effective doses of radiation to the bladder will be attained in the future without serious complications resulting from radiation of adjacent normal tissues The presented case clearly illustrates the unpredictable nature of carcinoma in general and emphasizes again the importance of using all the tools we have in the treatment of seemingly unresponsive malignant lesions

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EJACULATORY IMPOTENCE

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The inability to ejaculate during the sexual act has received little attention in the urological and psychiatric literature The urologist is not infrequently consulted to rule out an organic basis for this disorder The purpose of this publication is to report a case of ejaculatory impotence in detail and to describe the changes in the patient's personality as his ability to ejaculate returned to normal under psychotherapy

Sexual impotence in the male may present itself in various forms and grades of severity The most frequent types of impotence are 1) a decrease to complete absence of libido, 2) poor or inadequate erection to complete satisfactorily the sexual act, 3) premature detumescence before emission, 4) premature ejaculation, and 5) complete absence of ejaculation or ejaculatory impotence

There are many references in the urological and psychiatric literature discussing the etiology and treatment of the first four types of sexual impotence Impotence due to an inability to ejaculate has not appeared in the urological literature during the past 15 years In answer to a question directed to the Editor of the J A M A ,[1] three unnamed consultants in single paragraphs briefly discussed the question of "aspermia during intercourse," as a result of ejaculatory impotence All three emphasized the importance of the emotional factors in this uncommon but well recognized variety of impotence One of them stated that since psychogenic factors are predominant, a cure rarely can be accomplished without adequate psychotherapy Most of the references in psychiatric literature are credited to Dr Edmund Bergler,[2] who first described the psychodynamics of ejaculatory impotence in 1934 As a result of the predominance of pathological, oral character traits in such individuals, Dr Bergler coined the term, psychogenic oral aspermia, as a psychological corollary to the diagnostic label, ejaculatory impotence Usually the patient with this problem can sustain an erection almost indefinitely, and although the female partner may achieve a satisfactory orgasm, he himself fails to achieve the sexual climax When nocturnal emissions are present, it can be safely assumed that there is nothing intrinsically wrong with the reflex neuromuscular mechanism of ejaculation Some individuals with ejaculatory impotence may be able to masturbate with an emission This may represent an intermediary step to eventual recovery or another form of the illness Ejaculatory impotence may occur in individuals who have been potent for years but in whom emotional factors have intruded themselves As a rule these individuals are more easily treated by supportive measures than those

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[1] J A. M. A., Queries and Minor Notes **160** 249, 1956

[2] Bergler, Edmund The Basic Neurosis New York Grune & Stratton 1949 Psychogenic Oral Aspermia, pp 149–168

who have never experienced ejaculation during intercourse. The persistent failure to ejaculate represents a more deep-seated emotional disorder. Such patients are usually passive, emotionally immature, unable to accept responsibility and unable to be competitive or aggressive in a masculine way. In general they are frequently dependent, looking to parental figures for guidance and direction. Feminine and oral aspects of their personality are accentuated.

CASE REPORT

The patient was a 21-year-old tall, chubby, handsome, baby-faced, "dependent looking" male. He had been married nine months when he was referred by the urologist for psychotherapy with the presenting symptom of ejaculatory impotence. Although he had occasional nocturnal emissions, he never experienced an ejaculation in the waking state, even with masturbation. The most striking personality characteristics were his passivity, his need to be cared for, and his inability to accept responsibility for decisions. Oral traits were markedly exaggerated. He over-ate, over-talked, sucked his thumb, and during infrequent sex contacts with his wife emphasized kissing in his approach to her. He avoided all responsibility at home and at work and dependently looked to others to solve his problems. There was much pseudo aggressive behavior (blaming others for his own lack of competitiveness which generally led to failure), a frequent device of dependent personalities. Basically, he felt inadequate as a male and later emphasized the feminine aspects of his personality. His reaction to sex was pseudo-masculine, combining an erect penis without the ability to carry out the act and to give of himself in a mature way to his wife.

His father, whom he held in awe, was a successful businessman who had spent most of his time at work and little with his son. The mother, to whom the patient was pathologically bound, was seductive, markedly overprotective of her son and completely controlled the family. As a child the patient had many food fads, was easily upset and cried frequently. In response to any frustration or criticism he would withdraw to his room and suck his thumb, a habit he continued into adulthood. His mother would lie down in bed with her son almost nightly, kissing and hugging him until he went to sleep. This continued until adolescence. Although the patient started to date girls at an early age, it was more on a girl-to-girl basis. He had known his wife for several years and apparently enjoyed necking, kissing, and petting, but after marriage lost interest in sex. Psychological tests[3] corroborated the writer's impression of an immature, passive-dependent male who repressed overt aggression and had a need to cling to objects for love, support, and enjoyment. His intelligence was better than average. The tests also demonstrated a definite reversal of the normal masculine drive towards activity and independence and emphasized his feminine characteristics. The psychiatric impression was that of a personality trait disturbance, passive dependent type, with a psychophysiologic genitourinary reaction, ejaculatory impotence[4] Psychoanalytic psychotherapy was recommended and accepted by the patient, not only for his ejaculatory impotence, but also for his personality disturbance During the period of treatment the patient showed progressive changes both sexually and emotionally from a pre-adolescent level to that of a mature, adult male

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[3] Given by Libby Bass, instructor in Clinical Medical Psychology, Department of Neuropsychiatry, Washington University School of Medicine.

At first the patient looked to the therapist for answers to all his problems He wanted medication, sex instruction, and asked to be hypnotized to solve his sexual problem All of this was in accord with his passive dependent relationship to his parents He recognized his lack of sex interest as a continuation of an infantile pattern of behavior Early in treatment he began to experience sex interest in older depreciated women who were big breasted like his mother (much like the normal adolescent who diverts his sexual interest for his mother towards other women of a lower social level) Five months after treatment began, he was able for the first time to have a nocturnal emission following sexual fantasies with women as described above He went through periods of adolescent interest in hobbies, sports, and for the first time began to allow himself to enjoy "sexy" photographs and suggestive literature Toward the end of the first year he was finally able to masturbate with ejaculation This second phase of his developing maturity occurred at a point in treatment when he was feeling more able to participate in business without being totally dependent on his father The fact that his wife was in the hospital for diagnostic tests in reference to an unexplained fever offered him the symbolic freedom to experiment with masturbation from which he had refrained up to this time in therapy

At the end of this second phase of treatment the patient became anxious to discontinue therapy for although he still could not carry out normal sex relations, he now felt that he could use his semen, acquired by masturbation, to impregnate his wife, and thus outwardly he would be accepted as an adequate male There was even a more marked avoidance of sexual intercourse with continued interest in masturbation, again an adolescent trait It became obvious at this time that he felt his ejaculate was a danger both to his wife and to himself In addition, by ejaculating he would be deprived of something valuable which he did not want to give up, like the child who is reluctant to give up the breast Having achieved a partial success in therapy and unconsciously recognizing that further growth would lead to increased masculine responsibility, the patient became fearful and wished to break treatment This is a common phase in psychotherapy As this resistance in therapy was overcome, his adolescence gave way to a more integrated adult personality, and he began to take more responsibilities at home and at work It is interesting to note that as the patient developed a more masculine orientation the true picture of his wife emerged and she showed less interest in sex with definite symptoms of frigidity emphasizing the well known fact that usually immature women will marry such immature men.

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[4] *Diagnostic and Statistical Manual of Mental Disorders American Psychiatric Association*, 1952, pp 36–37
The diagnosis of personality trait disturbance applies to individuals who are unable to maintain their emotional equilibrium and independence under minor or major stress because of disturbances in emotional development Overt neurotic symptoms are relatively insignificant since the basic personality maldevelopment is the crucial distinguishing factor Such emotional disorders have been also known as character neuroses As a group they have good ego strength and in general lie between the overt neurotic and the normal person The passive dependent type is further characterized by helplessness, indecisiveness, and a tendency to cling to others as a dependent child to a supporting parent

As treatment continued the patient developed insight into the origins of his emotional problems. He now began to recognize that his mother's overprotection and seduction were a rejection of him as a male. This led to his infantile and feminine attitudes to compete with his sisters for his mother's love. The absence of his father's participation at home limited the patient's ability to identify himself with a masculine figure. Parallel with his improved personality came an increased sexual interest and finally a satisfactory completion of the sexual act. This came about in two stages. First he acted in a passive role while his wife carried out the active sexual movements astride him, but finally he was able to have sex relations in the usual male-female position.

Four years after psychotherapy the patient is still married and the father of two children. He has not had a recurrence of his symptoms, and the integrative masculine aspects of his personality have been maintained.

DISCUSSION

While ejaculatory impotence may be seen in late adolescence, it also may occur later in life following more normal sexual behavior when environment or intrapsychic factors act in a stressful way, as may also be true for premature ejaculation. Ejaculatory impotence differs psychologically from premature ejaculation which is seen more frequently in urologic practice. The patient with ejaculatory impotence reacts sexually by unconsciously withholding and refusing to give of himself while the patient with prematurity acts as if he doesn't want to refuse by giving immediately. In some ways they are similar. Both are forms of impotence in which organic factors play little or no role while psychological factors are most prominent. Since both disorders have a strong hysteriform character structure they may respond to supportive and suggestive therapy whether it be medical physical procedures, authoritative statements, or reassuring remarks. Such supportive procedures do not modify the basic personality of the patients. Although they may make what appears to be an adequate adjustment for some time, relapses may occur. More intensive psychotherapy is essential for those major pathological character traits which are the concomitants of the sexual dysfunction.

Urologists who see such patients in their office practice should after making a diagnosis evaluate the family and personal history. In selected patients friendly encouragement the use of ventilation and listening to a patient's discussion of his family situation may be of considerable help in modifying the disorder. Medication in general is to be considered as suggestive psychological therapy only and its use should be limited. In more resistant cases, since motivation is a potent force in psychotherapy, the urologist must prepare the patient adequately for psychiatric referral. The prognosis following adequate psychotherapy in cases of ejaculatory impotence as well as premature ejaculation is good. Since it is well known that sexual failure is a psychological defense (psychic masochism) of individuals with ejaculatory impotence, they will not voluntarily come for help until properly motivated by their physician

SUMMARY

A case of ejaculatory impotence treated by intensive psychoanalytic psychotherapy with a favorable outcome has been described The interesting phases of the emotional and sexual growth from a pre-adolescent period to that of a mature adult have been presented in detail Although it is recognized that the urologist treats many types of sexual disorders with supportive measures, the more difficult patients, of whom this patient is one, should be properly motivated and referred for psychotherapy

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SPERM GRANULOMAS INVOLVING THE TESTIS
REPORT OF TWO CASES

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Spermatic granulomas are a rare entity if one judges the number of cases reported to date. They are generally produced by sperm invasion of the wall of the epididymis or extravasation from a resected vas with a concomitant reaction of phagocytic and epithelioid cells. Frequently, spermatocele, trauma, infection or a therapeutic vas ligation predisposes. Spermatic granulomas in the testis itself are even rarer.

CASE REPORTS

Case 1. A. D. A., a 23-year-old white man, was first examined on November 28, 1956, with the complaint of sterility of five and one-half years' duration.

Examination revealed a normal male habitus and the positive findings were confined to the genitalia. Both testes were of normal size and consistency. The left vas deferens was indistinct and the right vas was not outlined whatsoever on palpation. The prostate was normal.

The laboratory tests of the seminal fluid on several occasions revealed azospermia in volumes of approximately 0.5 cc. Other laboratory tests such as the hemoglobin, urine analyses, and basal metabolic rate were normal. Biopsy of the testes and exploration of the excretory ducts were accomplished December 7, 1956. Neither right nor left vas was found. The right epididymis consisted of a caput major only, and the left epididymis was atrophic. Biopsies were taken from both testicles.

Microscopically many tubules were relatively normal, some of which showed atrophy with Sertoli cells remaining. One group of tubules showed disruption, and contained lymphocytic infiltration surrounding pools of sperm. Sperm containing phagocytes were also present. See figure 1.

Case 2. M. S., a 35-year-old white man (courtesy of Drs. H. Bodner and R. Myers), complained of a painful swelling of the right testis of two days' duration. His only significant past history was that of a therapeutic vasectomy performed in 1954.

Examination revealed a firm nodular area, approximately 1 cm. in diameter, in the region of the globus major of the right epididymis. On November 14, 1956 an orchiectomy was done and a diagnosis of a testicular germinoma made. In addition, the remainder of the testis showed granulomas all contained within pre-existent tubular structures. They were composed of epithelioid and giant cells with vacuoles that were presumably lipoid. The pattern was that of a pseudosarcoid granuloma and did not suggest the granulomas seen in germinomas. See figure 2.

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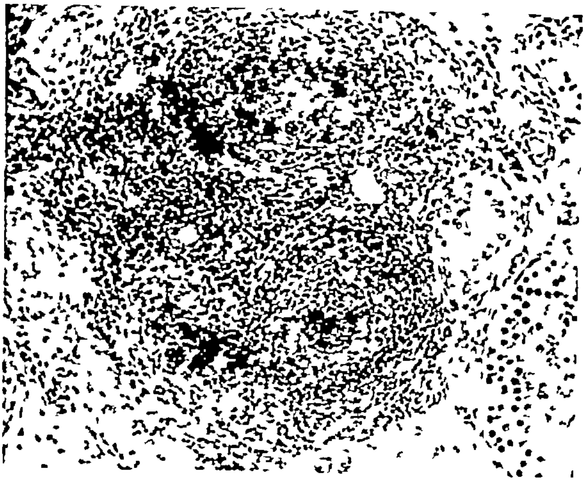

FIG 1 Case 1 Note inflammatory reaction with intratubular sperm and histiocytes × 170

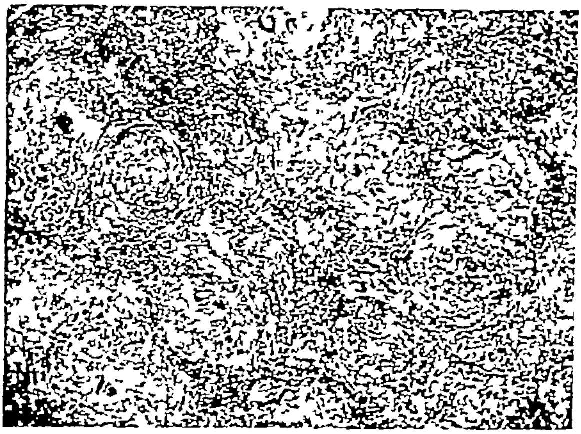

FIG 2 Case 2 Note pseudosarcoid tubercles in testicular tubules × 85

DISCUSSION

In the first case, the congenital absence of the vasa would of necessity predispose to intratubular stasis As regards the second case, in spite of the fact that granulomas are common in germinomas, it seems likely that the vas ligation produced tubular stasis which was responsible for the granuloma formation The fact that the individual granulomas were based on an individual tubular framework suggests that they had begun within the tubules unrelated to the tumor

In case 1 the lesion did not suggest typical granulomatous orchitis although in the second case there were similarities Possibly tubular sperm granulomas and granulomatous orchitis are related

Since approximately 30 per cent of infertile males reveal no known causative factors upon exhaustive examination, one might conjecture that internal obstructions within the testes or the excretory ducts may play a role It is most conceivable that granulomas within the conduits may provide ample obstruction, either partial or complete, to sperm flow With greater resort to the use of x-ray visualization of the epididymis as well as the vasa, one might clinically detect more of these cases We thank Drs Bodner and Myers for permission to use their case in this report

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SCROTAL AND TESTICULAR TEMPERATURE STUDIES IN PARAPLEGICS

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Hyperthermia in the scrotum has been postulated as one of the causal factors in the development of testicular atrophy among paraplegic patients[1] It has been suggested that in the paraplegic individual, as a consequence of injury to the sympathetic innervation of the testicular blood supply, a state of hyperemia and hyperthermia develops and precipitates testicular changes Environmental temperature in the scrotal cavity may also be influenced by the sweating mechanism of the organ, which is likewise under sympathetic control

The adverse effect of hyperthermia on the germinal epithelium is well known Moore has shown that higher temperatures account for the aspermatic condition of the undescended testis Using bulb thermometers, he found a difference of 7 5 degrees centigrade (13 5F) between the peritoneal cavity and the cavity of the scrotum in the rat[2] Similar studies by Badenoch in man showed that the average intraperitoneal temperature in the region of the iliac fossa was 2 2 degrees centigrade (3 9F) higher than the temperature in the scrotal cavity on the same side[3] Hotchkiss and MacLeod observed reduction in sperm count after fever therapy[4]

This investigation was undertaken to record temperature readings in the scrotum and testis of paraplegics and to determine whether the thermal environment within the scrotal cavity as gauged by the measurements obtained could conceivably account for the ensuing testicular degeneration

MATERIAL AND METHOD

The subjects for this study were adult male paraplegic patients undergoing rehabilitative therapy at Bellevue Hospital and the Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center Normal observations were obtained from a group of male adult patients who were apparently free from any neurologic disease or febrile disturbance

Scrotal and testicular temperatures were taken by means of 22 gauge hypodermic needle with a thermistor bead sealed in the tip and connected to a Wheatstone bridge circuit Scrotal cavity temperatures were taken by inserting the

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TABLE 1 *Temperature measurements from the mouth rectum arm thigh, scrotum and testis of paraplegic and normal men*

	Oral Temp °F	Rectal Temp. °F	Arm Temp. F	Thigh Temp. F	Scrotal Temp. F	Testis Temp F
			Cervical			
J M	96.5	96.1	97.7	96.8	90.05	90.5
S H	97.8	98.4	96.8	97.05	95.9	96.8
J D	97.0	97.1	96.8	96.8	91.4	93.2
L J	98.6	97.6	95.0	98.06	92.84	95.9
T M	98.4	97.0	93.9	98.6	97.34	—
B J	98.0	97.0	97.34	95.0	95.0	—
F N	98.0	98.6	94.55	94.55	96.8	96.8
C E	99.2	98.4	96.8	95.0	91.4	95.0
H S	99.4	99.8	98.6	98.6	99.5	—
H J	98.8	99.8	97.7	99.5	98.6	—
			Thoracic			
S G	98.0	98.8	96.8	95.0	91.4	92.6
B C	98.6	98.6	97.27	96.8	96.35	—
W J	99.2	99.8	99.05	97.25	97.70	96.8
G F	98.6	98.8	97.25	96.8	96.8	95.0
G J	98.0	98.0	98.6	99.5	—	90.3
H M	98.2	98.0	96.8	96.8	94.1	96.8
T G	97.8	98.0	98.6	97.7	97.7	94.1
M P	97.8	98.4	97.05	97.7	96.8	97.7
J J	97.1	99.6	99.5	99.5	97.05	97.7
A P	98.4	98.2	98.4	100.2	95.9	—
C T	97.8	98.5	95.25	95.9	94.41	95.0
B D	98.6	98.8	96.8	95.9	93.2	94.1
Z T	98.6	99.0	95.0	95.0	94.1	—
M J	97.6	98.2	95.0	94.4	93.8	91.4
M G	98.4	98.6	99.1	96.8	95.0	95.0
M C	98.6	98.6	98.06	98.06	95.0	97.34
			Lumbosacral			
F S	98.6	98.7	97.7	96.8	95.25	—
P C	97.6	98.0	93.2	94.1	93.2	—
R W	98.0	98.4	97.25	97.7	94.55	—
			Normal			
W R	99.4	100.2	100.4	97.7	96.8	—
C N	98.8	100.2	100.4	100.4	97.7	—
C P	98.2	99.4	97.7	99.5	93.2	—
J M	98.0	99.4	97.7	97.7	97.45	—
T 7	98.2	98.6	97.7	97.45	97.45	—
D D	98.8	99.0	100.4	97.7	96.8	—
T C	98.6	100.2	97.7	97.7	95.0	—
P A	98.6	100.2	99.5	99.5	96.8	—
J J	97.6	98.6	93.82	100.4	95.9	—
P M	98.8	99.0	98.6	96.8	96.8	—

needle through the intact scrotal skin with the tip as close to the surface of the testis as possible Testicular temperatures were measured by further inserting the needle into the gonadal mass so that its tip lay in the center

Concomitant temperature determinations were also obtained from the arm, thigh, mouth and rectum Arm and thigh temperatures were taken by inserting

TABLE 2 *Analysis of the deviation of rectal temperature from oral temperature in paraplegic and normal men*

Lesion	No of Patients	Mean F	Standard Deviation	Fisher t^2 value	Probability
Cervical	10	+ 09	87	10	*
Thoracic	16	− 41	63	6 60	05
Lumbosacral	3	− 30	17	9 00	05
Normal	10	− 98	57	31 40	01

(−) oral temperature less than rectal temperature
(*) probability < 1

TABLE 3 *Analysis of the deviation of subcutaneous thigh temperature from subcutaneous arm temperature in paraplegic and normal men*

Lesion	No of Patients	Mean F	Standard Deviation	Fisher t^2 value	Probability
Cervical	10	− 47	2 16	47	*
Thoracic	16	+ 32	1 15	1 22	*
Lumbosacral	3	− 45	1 00	59	*
Normal	10	− 14	2 67	00035	*

(−) arm temperature less than thigh temperature
(*) probability < 1

TABLE 4 *Analysis of the deviation of scrotal temperature from subcutaneous thigh temperature in paraplegic and normal men*

Lesion	No of Patients	Mean F	Standard Deviation	Fisher t^2 value	Probability
Cervical	10	−2 04	3 09	4 34	0 1
Thoracic	14	−1 73	1 65	8 8	0 01
Lumbosacral	3	−1 86	1 33	5 86	*
Normal	10	−2 09	2 09	9 9	0 05

(−) scrotal temperature less than thigh temperature
(*) probability < 1

TABLE 5 *Analysis of the deviation of testicular temperature from scrotal temperature in paraplegic men*

Lesion	No of Patients	Mean F	Standard Deviation	Fisher t^2 value	Probability
Cervical	10	−1 46	1 37	6 8	05
Thoracic	16	−0 05	1 18	0 01	*

(−) scrotal temperature less than testicular temperature
(*) probability < 1

the needle of the electronic thermometer obliquely into the subcutaneous tissue to the extent of one and a half inches A clinical thermometer was utilized for oral and rectal temperatures

RESULTS

Temperature readings from the mouth, arm, thigh, rectum, scrotum and testis of 29 paraplegic and 10 normal men are recorded in table 1

A comparison of simultaneously determined oral and rectal temperatures is shown in table 2 It will be noted from the calculated mean differences that except in the group with cervical lesions, oral temperature was significantly lower than rectal temperatures

The thermal gradients between arm and thigh temperatures are shown in table 3 The average differences varied in both directions and were of no statistical significance in any of the groups Thus, it appears that in spite of a spinal cord transection and its associated disturbances, subcutaneous temperature below the level of the lesion remains essentially unaltered

Temperature in the scrotum was cooler than in the thigh in both paraplegic and normal subjects (table 4) The variation was 2 04 degrees Fahrenheit in the cervical group, 1 73 degrees Fahrenheit in the thoracic group, 1 86 degrees Fahrenheit in the lumbosacral group, and 2 09 degrees Fahrenheit in the normal subjects These data indicate that the scrotal thermal environment in the paraplegic individual is not significantly different from that in nonparalyzed men

The relation between testicular and scrotal temperatures is shown in table 5 It was possible to measure testicular temperatures only in patients belonging to the cervical and thoracic group because the others had preservation of testicular sensations and could not tolerate the procedure It will be seen that testicular temperature is slightly warmer than scrotal temperature The same relation was found in normal men by other workers [5]

SUMMARY

Temperature measurements were taken from the scrotum, testis, arm, thigh, mouth and rectum of 29 paraplegic and 10 normal men A hypodermic needle with a thermistor device was utilized for scrotal, testicular, arm and thigh determinations and a clinical thermometer for the mouth and rectum

Oral temperature was significantly lower than rectal temperature in the groups studied Arm and thigh temperatures did not significantly vary from each other in both paralyzed and nonparalyzed subjects

Scrotal temperature in the paraplegic individual did not significantly differ from the normal Testicular temperature was slightly warmer than scrotal temperature in the paraplegic subjects studied

It appears that hyperthermia in the scrotum does not develop in paraplegic patients The testicular atrophy that develops in such individuals, therefore, has to be attributed to some other causal factors

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THE CLINICAL SIGNIFICANCE OF ABNORMAL PROSTATIC SECRETION

JOHN E BOWERS AND GORDON B THOMAS, B S

The purpose of this study was to correlate findings in gross, microscopic and bacteriologic examination of prostatic secretion and "prostatic" symptomatology in 100 unselected urological patients, in an attempt to establish standards of normality so that they may be applied to examination of the prostatic secretion in general practice Previous work has been equivocal and is not referred to for this reason Because it would seem that the problem of prostatic infection must lend itself to a statistical analysis it was deemed worthwhile to attempt to clarify the situation, particularly *with regard to the detailed findings of each individual specimen and the relation of the findings to the patient's symptoms at the time the specimen was acquired* It was hoped, at the onset of the study, that an analysis of these accumulated data would provide the answer to many of the questions which plague those who concern themselves with the constitutents of the prostatic fluid, i e , the significance to be attached to increased numbers of pus cells, to positive cultures, etc Before progressing far with the work it was obvious that symptomatology was invariably vague in character, lending an element of inaccuracy to the statistical analysis However, by expressing the findings as possibilities rather than percentages, it was felt that the conclusions would be of most aid to the practitioner who is faced with the problem in the individual patient

MATERIAL AND METHODS

The records of 100 male patients who had undergone routine studies to rule out possible prostatic infection were analyzed (table 1) Some of these had been referred with a diagnosis of prostatitis, but the majority had completely unrelated problems such as infertility, hydrocele or the like A complete examination of the external genitalia and abdomen was carried out on any new patient "Prostatic" symptoms at the time of each examination, before obtaining prostatic secretion, were noted The patient was instructed to partially empty his bladder, cleansing the urethra Vigorous prostatic massage was then carried out with the patient compressing his urethra between gauze pads The first drops of secretion were collected in dextrose tubes for culture (CPS) Microscopic examination was done on ther emaining secretion under a cover slip using the high dry lens The amount of prostatic secretion obtained was estimated and noted Then catheterization was carried out and culture was performed on a specimen of bladder urine (CU) In this manner a complete set of data referable to a single incident, the culture of the prostatic secretion (CPS), were made available This procedure was carried out on 97 occasions, and in addition 91 prostatic specimens were cultured without accompanying urine cultures, in 100 patients, making a total of 188 CPS and 97 CU available for study

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RESULTS

General data Cultures were made in a ratio of 2 CPS to 1 CU in 100 patients, 188 CPS were done, 97 of which were accompanied by CU, a total of 285 cultures Of 100 patients, 55 had one CPS, 24 had 2 CPS, 7 had 3 CPS, 8 had 4 CPS, 5 had 5 CPS and one had 7 CPS Of the same 100 patients, 66 had 1 CU, 14 had 2 CU, 1 had 3 CU and 19 had no CU performed

Table 1 shows the age distribution with relation to the presence or absence of "prostatic" symptoms in the 100 patients It will be noted that the age group 50–59 is preponderantly symptomatic, otherwise the age groups show equal numbers of symptomatic and asymptomatic patients

Approximately ¾ of 188 prostatic secretions yielded positive cultures, while only 1 in 10 urine cultures was positive Of 136 positive CPS, 42 per cent were accompanied by negative CU, 8 per cent by positive CU Of 52 negative CPS, 52 per cent were accompanied by negative CU, 2 per cent by positive CU CU was not performed with 50 per cent of positive CPS, 46 per cent of negative CPS Of 100 patients 74 showed positive CPS at some time during their investigation while 26 were always negative Of the 81 patients having CU 13 per cent showed positive CU at some time while 87 per cent were always negative Of the 81 patients who had one or more CPSCU done concurrently, 80 per cent had 1 CPSCU, 18 per cent had 2 CPSCU and 2 per cent had 3 CPSCU

SYMPTOMS

Of 100 patients 56 had symptoms at some time during the investigation while 44 patients never had symptoms Of 188 CPS 45 per cent were accompanied by "prostatic" symptoms at the time the specimen was taken while 55 per cent had no symptoms Forty-two per cent of 136 positive CPS, 54 per cent of 52 negative CPS, 92 per cent of 12 positive CU and 48 per cent of 85 negative CU were accompanied by symptoms Thirty-six per cent of 91 CPS which were done without concurrent CU were accompanied by symptoms

Of the various combinations of positive and negative prostatic and urine cultures, 45 per cent of 58 CPS positive CU negative, 59 per cent of 27 CPS negative CU negative, 92 per cent of 11 CPS positive CU positive, 100 per cent of one

TABLE 1 *Distribution of symptomatic and asymptomatic patients with respect to age group 100 patients*

Age Group	Symptoms	No Symptom	%
yrs	*patients*	*patients*	
20–29	11	17	28
30–39	16	15	31
40–49	9	9	18
50–59	14	1	15
60–69	4	2	6
70 and over	2	0	2
Total	56	44	100

CPS negative CU positive were accompanied by symptoms Thirty-two per cent of 67 CPS positive and 46 per cent of 24 CPS negative, with which CU were not done concurrently, were accompanied by symptoms

Of 136 positive cultures of prostatic secretion 15 per cent were accompanied by acute symptoms, 27 per cent by chronic symptoms and 58 per cent by no symptoms Of 52 negative cultures of prostatic secretions 18 per cent were accompanied by acute symptoms, 36 per cent by chronic symptoms and 46 per cent by no symptoms Of 12 positive urine cultures 50 per cent were accompanied by acute symptoms, 42 per cent by chronic symptoms and 8 per cent by no symptoms Of 85 negative urine cultures 18 per cent were accompanied by acute symptoms, 30 per cent by chronic symptoms and 52 per cent by no symptom Of 91 prostatic cultures with which no urine culture was done 9 per cent were accompanied by acute symptoms, 27 per cent by chronic symptoms and 64 per cent by no symptoms

Of the various combinations of positive and negative prostatic and urine cultures 14 per cent of 58 CPS positive CU negative, 26 per cent of 27 CPS negative CU negative, 46 per cent of 11 CPS positive CU positive, and 100 per cent of one CPS negative CU positive were accompanied by acute symptoms, 31 per cent of 58 CPS positive CU negative, 33 per cent of 27 CPS negative CU negative, and 46 per cent of 11 CPS positive CU positive were accompanied by chronic symptoms, while 55 per cent of 58 CPS positive CU negative, 41 per cent of 27 CPS negative CU negative and 8 per cent of 11 CPS positive CU positive were accompanied by no symptoms Of 67 CPS positive with which no urine culture was done concurrently 10 per cent were accompanied by acute symptoms, 22 per cent by chronic symptoms and 68 per cent by no symptoms Of 24 CPS negative with which no urine culture was done concurrently 4 per cent were accompanied by acute symptoms, 42 per cent by chronic symptoms and 54 per cent by no symptoms

Of 81 patients having a urine culture done concurrently with a culture of prostatic secretion, 12 per cent had CPS positive CU positive at some time, 30 per cent always had CPS negative CU negative and 58 per cent were irregular (CPS positive CU negative etc) Of 10 patients showing CPS positive CU positive at some time, 50 per cent had acute symptoms at some time, 40 per cent had chronic symptoms only while 10 per cent had no symptoms at any time Of 24 patients always showing CPS negative CU negative when done together, 28 per cent had acute symptoms at some time, 28 per cent had chronic symptoms only, while 44 per cent had no symptoms at any time Of 47 irregular patients 19 per cent had acute symptoms at some time, 30 per cent had chronic symptoms only, while 51 per cent had no symptoms at any time Of 19 patients having CPS done without concurrent CU, 21 per cent had acute symptoms at some time, 32 per cent had chronic symptoms only, while 51 per cent had no symptoms at any time

Of 97 cultures of prostatic secretions done concurrently with 97 urine cultures, 52 per cent were accompanied by symptoms while 48 per cent were not accompanied by symptoms

Of 85 cultures of prostatic secretions accompanied by symptoms 34 per cent were accompanied by acute symptoms and 66 per cent were accompanied by chronic symptoms

Bacteriology Of 136 positive cultures of prostatic secretions 69 per cent grew coliform organisms, 13 per cent grew hemolytic Streptococcus, 10 per cent grew non-hemolytic Streptococcus and 8 per cent grew Staphylococcus or Proteus And of 12 positive urine cultures 92 per cent grew coliform organisms while 8 per cent grew hemolytic Streptococcus

Fifty-one per cent of prostatic cultures yielding coliform bacteria, 36 per cent of those yielding non-hemolytic Streptococcus, 24 per cent of those yielding hemolytic Streptococcus and 54 per cent of negative prostatic cultures were accompanied by symptoms at the time cultures were taken Bacteria found and not mentioned above were not associated with symptoms Of 10 patients yielding 11 CPS positive CU positive 75 per cent pure coliform and 20 per cent mixed cultures had accompanying symptoms (50 per cent acute) while 5 per cent of the mixed cultures had no accompanying symptoms Of 11 patients having 12 positive urine cultures 90 per cent were coliform accompanied by 50 per cent acute, 30 per cent chronic and 10 per cent no symptoms, 10 per cent of patients yielding hemolytic Streptococcus were accompanied by chronic symptoms

Of 97 prostatic cultures done concurrently with urine cultures 27 CPSCU showed no growth in either culture Of the 70 CPSCU showing growth 71 per cent were predominantly coliform, 8 per cent hemolytic streptococcus, 7 per cent non-hemolytic Streptococcus and 14 per cent mixed or Proteus, etc

Microscopic findings Of 188 prostatic secretions examined microscopically by high dry lens (43 ×) concurrently with culture of the same secretions, 62 per cent showed less than 10 white blood cells per field (normal), 12 per cent 10 to 20 WBC per hpf (1+), 10 per cent 20 to 50 WBC per hpf (2+), 7 per cent 50 to 100 WBC per hpf (3+) and 9 per cent more than 100 WBC per hpf (4+) Approximately 60 per cent of those secretions classified as normal, progressing to 40 per cent of those classified 4+, were accompanied by no symptoms Regardless of microscopic findings 75 per cent of 188 prostatic cultures were positive, when grouped according to concurrent microscopic examination of the secretions Two thirds to three-fourths of positive cultures of prostatic secretions yielded coliform organisms regardless of findings on microscopic examinations of the secretions Hemolytic Streptococcus, non-hemolytic Streptococcus, Staphylococcus and Proteus followed in that order

Of 85 microscopic examinations of prostatic secretions accompanied by symptoms the percentage of acute symptoms varied from 11 per cent to 50 per cent when grouped according to microscopic findings, a rather wide range The number of cases was small and there appeared to be no relation between the microscopic findings and the type of symptoms present Similarly when grouped according to presence or absence of symptoms, severity of microscopic abnormalities and results of culture of each prostatic secretion no diagnostic correlation could be found, as in any microscopic classification there was a tendency for symptomatic negative cultures to exceed symptomatic positive cultures in number The number of cases became very small when attempting a further breakdown into type of symptoms but findings on microscopic examination appeared to have somewhat more influence than culture results on whether symptoms were acute or chronic Also, when grouped according to the presence or absence of symptoms, microscopic findings and the type of organism found in positive culture of each prostatic secretion, one-fourth to one-half of coliform or other positive prostatic cultures were accompanied by symptoms no matter what was found on microscopic examination of this secretion

Quantity of secretion Approximately two-thirds of the prostatic secretions were considered profuse, one-third scant in amount Approximately two-thirds of the positive prostatic cultures and two-thirds of the negative prostatic cultures were associated with profuse secretion When grouped according to microscopic findings no correlation was found with the quantity of prostatic secretion, approximately two-thirds of prostatic secretions were profuse in each group When grouped according to the type of organism found in positive cultures approximately two-thirds of positive prostatic cultures were associated with profuse secretion, regardless of the type of organism found

One-third of 29 prostatic secretions accompanied by acute symptoms were considered scant, two-thirds profuse in amount One-third of 56 prostatic secretions accompanied by chronic symptoms were considered scant, two-thirds profuse in amount One-third of 103 prostatic secretions accompanied by no symptoms were considered scant, two-thirds profuse in amount Similarly when grouped according to the results of prostatic culture and microscopic examination of the secretion and quantity of secretion generally the ratio of one-third scant to two-thirds profuse will be maintained The ratio is also maintained when the data are grouped according to the organism found in positive prostatic cultures, presence or absence of symptoms, microscopic findings and amount of secretion, and it is maintained in a survey of the 52 negative prostatic cultures There was no marked difference with respect to the presence or absence of symptoms between the "scant" and "profuse" groups, while taking into account all of the other factors such as microscopic findings and culture results

Results of therapy When the results of cultures of prostatic secretions and microscopic findings on examination of this prostatic secretion are considered in the 45 patients who had more than one culture, 53 per cent were improved by treatment, 42 per cent were unimproved and 5 per cent were made worse

Considered findings on microscopic examination of the prostatic secretions only, the same relation prevails Fifty-three per cent were improved, 33 per cent unimproved and 14 per cent made worse

DISCUSSION

The following generalizations are derived from a survey of the preceding data

1) The chances are 3 to 1 that any one of a series of cultures of prostatic secretions will be positive, by our culture technique The chances are 3 to 1 that, regardless of findings on microscopic examination, any prostatic secretion will yield a positive culture, and in these positive cultures the chances are 3 to 1 that

the organism found will be coliform Thus the findings on microscopic examination appeared to have no relation to the results of culture of the prostatic secretion (Two-thirds of 188 secretions were normal microscopically, one-third contained more than 10 white blood cells per high power field)

2) The chances are 50 50 that a subject will have symptoms remotely referable to the prostate gland regardless of findings on microscopic examination of the prostatic secretion If symptoms exist the chances are 2 to 1 that the symptoms will be chronic, regardless of findings on microscopic examination of the prostatic secretion (Of 85 prostatic specimens accompanied by symptoms 29 (34 per cent) were acute and 56 (66 per cent) were chronic symptoms) Thus findings on microscopic examination, culture results and amount of secretion had no bearing on the presence or absence of symptoms

3) The chances are 50 50 that a prostatic secretion yielding a culture positive for coliform organism will be accompanied by symptoms (The chances are even that a prostatic secretion yielding no growth will be accompanied by symptoms) The chances are 1 in 3 that a secretion yielding a positive culture for hemolytic or non-hemolytic Streptococcus will be accompanied by symptoms Thus the type of organism found would appear to have little influence on the presence or absence of symptoms

4) The chances are 1 in 6 that a prostatic secretion will be accompanied by acute symptoms, 1 in 3 that a prostatic secretion will be accompanied by chronic symptoms and 1 in 2 that a prostatic secretion will be accompanied by no symptoms regardless of microscopic findings, culture results, organism found and amount of secretion Hence microscopic findings, culture results, organism found and amount of prostatic secretion have no relation to the type of symptoms present

5) The chances are 2 to 1 that, regardless of microscopic findings, culture results or type of organism found, any prostatic secretion will be profuse in amount (Of 188 prostatic secretions two-thirds were considered profuse, one-third scant in amount) Thus the amount of secretion has no clinical significance

6) The chances are almost 100 per cent that a postive urine culture will be accompanied by symptoms and the chances are even that a negative urine culture will be accompanied by symptoms

The chances are even that a positive urine culture will be accompanied by acute or chronic symptoms, while the chances are 1 in 6 that a negative urine culture will be accompanied by acute symptoms, 1 in 3 that a negative urine culture will be accompanied by chronic symptoms, and 1 in 2 that a negative urine culture will be accompanied by no symptoms

7) The chances are 3 to 1 that any male patient will have a positive culture of prostatic secretion and the chances are 1 in 10 that any male patient will have a positive urine culture at some time during the period of his investigation Considering findings on microscopic examination and culture of the prostatic secretion the chances are even that a patient will be improved and the chances are 1 in 10 that he will be made worse by conventional therapy

SUMMARY

In a group of unselected male urological patients the odds are 1 in 3 that a given prostatic secretion will show an abnormal number of white blood cells on microscopic examination If abnormal, there is an equal chance that the secretion will be 1, 2, 3 or 4 plus in quantity of pus cells

Findings on microscopic examination of prostatic secretion, type of organism found on culture of prostatic secretion and amount of secretion obtained by prostatic massage appear to have no bearing on presence or absence or type of symptoms ordinarily attributed to prostatic infection

If the prostatic secretion be cultured the odds are 3 to 1 that the culture will be positive regardless of whether the patient has symptoms, or whether the subject has normal or abnormal prostatic secretion on microscopic examination If the patient has a positive culture the chances are 3 to 1 that the organism found will be coliform

Microscopic examination and culture of the prostatic secretion would appear to be equally inaccurate in the diagnosis of *symptomatic* prostatic infection, since it is difficult to correlate the usual evidence for infection with chronic symptomatology

Prostatic infection per se is felt to be relatively common Persistently positive cultures of prostatic secretion would seem to indicate a possible "focus of infection" or source of systemic toxicity, and should be converted to negative cultures by conventional modes of therapy

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THE CYTODIAGNOSIS OF PROSTATIC CARCINOMA A FOLLOW-UP STUDY

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The search for accurate means of diagnosing cancer at an early stage continues In recent years, exfoliative cytology has gained widespread popularity as an applicable laboratory procedure The microscopic examination of body fluids for cancer cells has provided the physician with a technique whereby he has been able to diagnose carcinoma of the uterine cervix at an early, and often curable, stage Frequently, a positive cytological report precedes any clinical evidence of this disease In other situations, it provides ready confirmation of suspicions aroused at the time of pelvic examination and also a simple means of screening large populations for an all too frequent form of malignancy It is for these reasons that exfoliative cytology has received its widest application and greatest acclaim in the field of gynecology

However, there is considerable evidence available that this technique has provided an aid to the diagnosis of the hidden primary lesions of pulmonary and gastric carcinoma, as well as to the metastatic seeding of the pleural and peritoneal surfaces At present, most large cytology laboratories examine material from the aforementioned sources as well as breast secretions, duodenal washings and almost any other body fluid obtainable A further indication of the general acceptance and recognition of usefulness of exfoliative cytology is the announcement that candidates for the American Board of Pathology are required to be familiar with the techniques of collection, preparation and interpretation of smears [1]

In spite of the acceptance of exfoliative cytology as a useful adjunct to the diagnosis of malignancy, there has been considerable controversy over its application to the diagnosis of prostatic carcinoma Some investigators and authors have stated that it is not a useful technique, and caution that collection methods may actually disseminate the disease [2-7] The relatively high incidence of prostatic

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TABLE 1 *Cytologic criteria of malignancy*

1 Variation in size and shape of nuclei
2 Hyperchromatism
3 Crowding of cells and overlapping of nuclei (in sheets)
4 Bizarre, irregular nuclei
5 Chromatin stippling and patches
6 Single large or multiple nucleoli with altered nucleoli nuclear ratio
7 *Mitotic figures (rarely seen)*
8 Cast-like cell groupings

carcinoma is familiar to all urologists and the need for more accurate diagnostic methods is obvious One cannot hope to achieve the accuracy in diagnosis with this method that is realized in cervical carcinoma, since a specimen from the latter lesion can be obtained under direct vision The comparison should be made with existing diagnostic methods for the disease considered Ideally, open perineal biopsy is the procedure of choice in the case of the suspicious prostate However, this requires hospitalization and therefore is not feasible as a large scale office screening method Therefore, one must rely upon the examining finger, x-rays, phosphatase studies, punch biopsy, and exfoliative cytology to offer an aid to diagnosis prior to major surgical intervention and treatment

For the past eight and one-half years, our laboratory has been concerned with the application of exfoliative cytology to the diagnosis of prostatic carcinoma During this period, a total of 10,410 slides was examined on 2,445 patients in the age range in which this lesion is most prevalent In practically every instance, the specimens were screened and interpreted by the same cytologist As might be expected, the ease and accuracy of interpretation increased with the experience of the examiner Early in the study, direct organ smears obtained at the operating table and in the autopsy room were studied to gain familiarity with cell types which might be encountered in the specimens obtained from patients

COLLECTION AND PREPARATION OF MATERIAL

The specimens for examination were obtained by prostatic massage in practically every instance The patient preferably was not on indwelling catheter drainage or hormone therapy Occasionally, the spun sediment of the first voided urine after massage was examined in those cases in which massage was unyielding of secretion It was the impression of the clinicians involved that routine massage creates no demonstrable increase in the spread of the disease or over-all morbidity In fact, a review of cases in which radical perineal prostatectomy was performed on patients from this clinic yielded survival rates which compared very favorably with other such series reported [8] Most of these patients had been subjected to diagnostic prostatic massage prior to surgery and, in many cases, repeated massage

Adequate specimens are most readily obtainable by moderate lateral to medial digital pressure on the prostate followed by a milking compression down the median furrow to the region of the membranous urethra An effort is made to

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[8] Scott, W W An evaluation of endocrine control therapy plus radical perineal prostatectomy in the treatment of selected cases of advanced carcinoma of the prostate followed five or more years J Urol , 77 521, 1957

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TABLE 5. *Follow-up distribution of "false negative" prostatic smears, January 1, 1949–July 1, 1957*

	Unsatisfactory Specimen	Quantity Not Sufficient	One Negative Smear (1.2)	More Than One Negative Smear
No. Cases	31	11	19	16
%	40.3%	14.3%	24.7%	20.8%
Total No. False Negative = 77				

the patients who had been discharged with the diagnosis of "carcinoma of the prostate" during the same period without recorded evidence of positive cytology. Most of these cases represented proven carcinoma by the same standards previously described. Table 5 summarizes the breakdown of the 77 cases in which specimens for cytologic examination were obtained, making up the "false negative" group. Many of the patients from whom unsatisfactory specimens were obtained were on constant catheter drainage, hormone therapy or the material had been unsatisfactorily prepared. An inherent shortcoming of the technique is illustrated in the "quantity not sufficient" group. This inability to obtain adequate representative secretion for interpretation is a problem that applies to some patients and occasionally to some examiners.

DISCUSSION

Based on these data accumulated over an eight and one-half year period, we feel that the prostatic smear does offer a useful adjunct to the diagnosis of prostatic carcinoma. The valuable information obtained from this laboratory procedure used in conjunction with clinical impression, x-ray reports, phosphatase studies, and biopsy should give maximum accuracy of diagnosis. We are presently evaluating the additional technique of determining the prostatic acid phosphatase which we consider to be a more accurate and sensitive measure than the total serum acid phosphatase.

The specimen for cytologic examination may be readily collected at the time of the patient's first visit and repeated as needed. On the average, two specimens were obtained by massage per patient in this series. Since most patients with questionable prostatic lesions were examined at least twice as a diagnostic procedure, specimens were readily obtainable during these examinations. The accuracy of the technique definitely increases with repeated specimens but it in no way should be used as a tool of procrastination.

In those cases where radical surgery is indicated or may be possible after hormone control therapy, a biopsy should be obtained as soon as possible. Exfoliative cytology may help to determine which cases should be biopsied, by adding a further bit of evidence to a faint clinical suspicion. Another application is in the confirmation of other diagnostic tests in the debilitated patient who would not be biopsied or the patient with evidence of metastases prior to instituting hormone therapy or performing orchiectomy. When used as a screening procedure, a few cases of unsuspected carcinoma may be detected.

As is the case in any such laboratory procedure, the accuracy increases with the of the prostate in tissue removed at the time of surgery or autopsy Patients in the "definite evidence of carcinoma" category presented with a clinically characteristic, stony-hard, fixed gland often extending beyond the capsule and responding to some form of endocrine therapy, x-ray evidence of metastases from prostatic carcinoma, and/or markedly elevated serum phosphatase studies Most of the cases in this group had two or more of these criteria

In many instances, patients presented with findings on rectal examination, which were suspicious but not sufficiently positive to warrant an open perineal biopsy, and on whom all other studies carried out were negative or inconclusive for the diagnosis of carcinoma of the prostate These cases are tabulated in the "?- carcinoma" group Many of these patients are undergoing further evaluation or have been lost to further follow-up study

The "false positive" and "clinical data insufficient or absent" categories are self-explanatory classifications In this study, the former grouping represents those cases in which a positive smear was *not* supported by any other positive evidence of carcinoma on evaluation Not all of these patients have had surgical or autopsy material for histological examination The latter group includes cases which had to be omitted because of lack of follow-up information

Table 4 illustrates the data presented in table 3 broken down into per cent The cases of insufficient clinical data were omitted and those patients with histological or other "definite evidence of carcinoma" were grouped into the "proven carcinoma" category With this formula, class 3 offered an accuracy of 46 7 per cent, class 4, 83 8 per cent, and class 5, 97 per cent with a false positive incidence as noted

In an effort to determine how often the smear is negative in the presence of malignancy, an additional 306 hospital records were examined This comprised

TABLE 3 *Follow up study of suspicious (3) and positive (4 & 5) prostatic smears, January 1, 1949–July 1, 1957*

Classification	No of Patients	Histologically Proven Carcinoma	Definite Evidence of Carcinoma (Clinical X ray Laboratory)	?Carcinoma	False Positive	Clinical Data Insufficient or Absent (Omitted)
3	70	15	13	19	13	10
4	159	66	63	14	11	5
5	67	36	28	2	0	1
Total	296	117	104	35	24	16

TABLE 4 *Follow up distribution (%) of suspicious (3) and positive (4 & 5) prostatic smears January 1, 1949–July 1, 1957*

Classification	% Proven Carcinoma	% ?Carcinoma	% False Positive
3	46 7	31 7	21 7
4	83 8	9 1	7 1
5	97 0	3 0	0
Combined class 4 & 5 = 87 7% proven			

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URETHRAL STRICTURE FOLLOWING TRANSURETHRAL RESECTION OF THE PROSTATE

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One of the common sequelae of transurethral resection of the prostate is urethral stricture, particularly of the meatus.[1] Stricture has been reported in 20 per cent of these cases.[2] The pathology of strictures is a proliferation of fibroblasts in the tunica propria wherein the elastic tissue and muscle fibers are destroyed and replaced by fibroblasts. In inflammatory strictures this is also accompanied by infiltration of leukocytes.[3]

These strictures arise not only from trauma incident to the passage of endoscopic instruments and the caliber of these instruments in relation to the size of the urethra but to infection. Many of these patients have pyuria or prostatitis in the preoperative phase. Urinary tract infections are common after constant drainage by inlying catheters such as is customary following transurethral resection. The route of entry here is from the outside up the fluid-filled space between the catheter and the urethral mucosa.[4]

Cortisone and cortisone analogues depress fibroplasia, capillary growth and ground system proliferation.[5, 6] Scheinberg and Saltzstein[9] found cortisone and corticotrophin reduce the incidence of intra-abdominal adhesions. Stinchfield[10] reported cortisone prevented excessive fibrous tissue in arthroplastic procedures. Rosenberg and associates[11] stated that cortisone diminished the tendency toward scar tissue contracture in experimental lye strictures of the esophagus.

In the field of urology Baker and associates[12] noted that cortisone had no effect on uninfected wound healing in ureterovesical anastomosis. A significant reduction in the occurrence of secondary stricture due to infection was found in

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experience of the personnel involved This includes the clinician who obtains the specimen, the laboratory technicians who stain the slides, and the cytologist who interprets them Over the years, we have gained confidence in our convictions and have learned to appreciate and to respect the information which may be obtained from the microscopic evaluation of prostatic secretion for the presence of desquamated malignant cells

SUMMARY

An eight and one-half year follow-up study is presented on the application of the prostatic smear to the diagnosis of prostatic carcinoma During this period, 10,410 slides on 2,445 patients were examined In this group, there were 296 cases with class 3, 4, or 5 smears which were reviewed and classified A class 3 or suspicious report represented an accuracy of 46 7 per cent and a positive cytologic report (4, 5) correlated with an 87 7 per cent accuracy A breakdown of "false positive" and "false negative" reports is also presented

prior to surgery, had another and fatal cerebrovascular accident on the tenth postoperative day One patient expired at home on the eighth postoperative day of acute pulmonary embolus

Associated surgery performed was as follows Suprapubic cystostomy 5, litholapaxy 4 bilateral orchiectomy 16, bilateral vas ligation 105, internal urethrostomy 3, inguinal hernia repair 1, meatotomy 143, and insertion of radium needles 1

The largest amount of prostatic tissue resected in one sitting was 90 gm, the smallest 5 gm, with an average weight of 26 gm per resection Pathological diagnosis of benign hyperplasia was made in 126 Forty of these had associated chronic prostatitis Thirty-three patients had carcinoma of the prostate

Preoperative urinalysis was normal in 95 patients, 50 had pyuria and 14 gross hematuria Nine patients had vesical calculi Sixty-seven patients were in acute urinary retention when first seen Of the remaining 106 patients, residual urine varied from none to 2000 cc with an average residual of 149 cc

Twelve patients had urethral strictures prior to surgery Of these, six were in the group in which hydrocortisone was not utilized Location of the stricture here was as follows Meatal 2, pendulous 3, and posterior urethral 1 The two patients with meatal stenosis had meatotomies done at the time of transurethral resection and meatal strictures did not redevelop postoperatively Those with strictures in the pendulous and posterior urethra preoperatively acquired these same strictures postoperatively despite urethral dilation at the time of surgery Three of these patients had normal urinalysis preoperatively One had gross hematuria and chronic prostatitis

Location of the preoperative stricture in the six patients in whom hydrocortisone ointment was utilized was as follows Meatal 2, pendulous 4 Again, the two with meatal stenosis had meatotomies and did not reform a stricture postoperatively Of the four strictures in the pendulous urethra, three reformed postoperatively despite urethral dilatation at the time of surgery in all of them and internal urethrotomy in one One pendulous urethral stricture did not reform postoperatively This patient had pyuria preoperatively which disappeared following transurethral resection In addition, internal urethrotomy was performed at the time of resection

A total of 26 strictures were found postoperatively Fourteen of these were in the non-hydrocortisone ointment group giving an incidence of 6 per cent Twelve occurred in the hydrocortisone group for an incidence of 6.2 per cent

Location of stricture in the non-hydrocortisone group was as follows Meatal 6, pendulous 4 penoscrotal 3, and vesical neck 1 Preoperative urinalysis was negative in 6 contained pyuria in 5 and gross hematuria in 3 Pathological diagnoses were Benign hyperplasia 12, carcinoma 2 and associated prostatitis 5 A two stage resection was performed on 2 patients of this group

In the hydrocortisone group, strictures were located as follows Meatal 6, pendulous 5 posterior urethral 1 Preoperative urinalysis was normal in 8 and showed pyuria in 4 Pathological diagnoses were Benign hyperplasia 11, carciureterointestinal anastomosis Teasley[13] and Bodner and associates[14] independently reported that cortisone injected directly into the plaques of Peyronie's disease caused regression of the plaques Byrne[15] treated patients having urethral strictures with oral cortisone and obtained encouraging results Bonner and associates[16] injected hydrocortisone directly into the strictured area of the urethra with excellent effect

In an attempt to reduce the incidence of postoperative urethral stricture following transurethral resection of the prostate, we decided to apply hydrocortisone ointment topically to the urethral mucosa

METHOD

The ointment used contained 25 mg of hydrocortisone acetate, 5 mg of neomycin sulfate, 0 2 mg methylparaben, and 1 8 mg of butylparahydroxybenzoate per gram * Patients resected from January 1955 to February 1956 served as a control group In these, instruments and catheters were lubricated with an ordinary water-soluble jelly In the group of resections from March 1956 to May 1957, the urethral catheters inserted at the conclusion of surgery were liberally coated with the hydrocortisone ointment A small number of unselected patients in the latter period did not have applications of hydrocortisone ointment, primarily because it was not readily available in the operating room at the time These cases were added to the control group for statistical purposes Prostatectomies performed by surgical routes other than transurethral have been excluded from this study Several other factors possibly causing urethral stricture were concomitantly analyzed

RESULTS

A total of 173 transurethral resections of the prostate were performed on 159 patients Hydrocortisone ointment was used in 75 patients and not utilized in 84 In 14 patients two stage resections were done One hundred fifty-three patients were white and six Negroes The oldest person was 86 years, the youngest 43, an average age of 70 years Five deaths occurred One patient with arteriosclerotic heart disease had acute cardiac arrest during surgery Thoracotomy with cardiac massage was instituted, but the patient expired three hours after the heart resumed beating One patient had a fatal acute coronary occlusion on the second postoperative day One patient died on the fifth postoperative day of overwhelming septicemia not responding to a great variety of antibiotics One patient, who had had a cerebrovascular accident with hemiplegia one month

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* Neo-cortef ointment 2 5 per cent

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formed through an external urethrotomy Too few internal urethrotomies were performed for a conclusion to be drawn This method deserves further study

Pulling the inflated balloon of the urethral catheter downward under tension results in a slightly increased incidence of stricture This should be avoided where hemostasis can be obtained without this procedure

CONCLUSIONS

Hydrocortisone ointment applied topically will not prevent urethral strictures following transurethral resection of the prostate Prophylactic meatotomy will reduce the incidence of postoperative meatal stricture Putting urethral catheters under tension is undesirable where hemostasis can be obtained otherwise noma 1, and associated prostatitis 1 A two stage resection was performed in 1 patient in this group

Of the 26 patients in whom postoperative strictures developed, 10 were in acute urinary retention when first seen Residual urine in the remainder ranged from a minimum of 10 cc to a maximum of 600 cc with an average of 116 cc The largest amount of tissue resected in one sitting was 72 gm , minimum 6 gm and average 24 gm

Of the 12 patients who acquired postoperative meatal strictures, nine had prophylactic meatotomies at time of resection and hydrocortisone ointment was also utilized in 5 Of the three in whom no prophylactic meatotomy was done, hydrocortisone ointment was applied in one case

In those patients where capsular veins were opened and bleeding could not be readily controlled by fulguration, the indwelling catheter was pulled down under moderate tension and taped to the thigh This procedure was necessitated in 33 resections In seven of these postoperative urethral strictures developed

Postoperatively all patients had cloudy urine All were treated with various urinary antiseptics, usually one of the sulfonamides While one patient with a neurogenic bladder had a postoperative residual urine of 300 cc, the average post operative residual urine was 7 cc

DISCUSSION

It is apparent that hydrocortisone ointment applied topically does not reduce the incidence of postoperative urethral stricture following transurethral resection In the treatment of Peyronie's disease, it was found necessary to inject the drug directly into the fibrous plaque for the best results For the treatment of urethral strictures, the injection must be into the tunica propria Oral administration of hydrocortisone has been less satisfactory Apparently hydrocortisone applied topically, particularly in a non-water soluble base, will not traverse the mucous membrane in sufficient quantities to affect the underlying tissues

Surprisingly cases with preoperative pyuria did not show greater occurrence of postoperative stricture This is probably due to the fact that all cases were treated with one of the sulfonamides or antibiotics postoperatively Also urinary retention, whether acute or chronic, had no effect on the incidence of postoperative stricture

Two stage transurethral resections did not result in more postoperative strictures nor was the weight or amount of tissue resected a factor The type of pathological process, whether benign hyperplasia, carcinoma of the prostate or chronic prostatitis, did not influence the outcome of stricture

Meatotomy, while not preventing postoperative meatal stricture, did reduce its occurrence Since this is a simple procedure, it appears desirable as a prophylactic measure Preoperative strictures, other than meatal, will usually be aggravated postoperatively These patients probably should have the resection per-

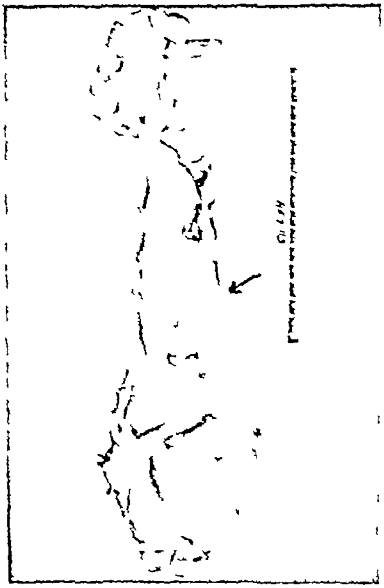

FIG 1 Solitary right kidney draining into retroperitoneal ectopic left seminal vesicle. Note duct-like structure arising from lower pole of kidney and opening into seminal vesicle (arrow) Bladder shows one ureteral opening on right

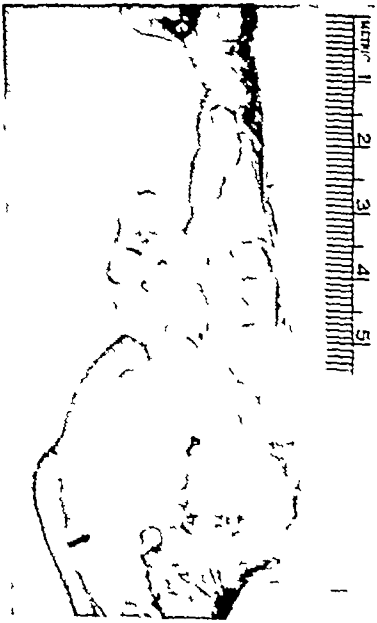

FIG 2 Close up view of bisected ectopic left seminal vesicle and vas deferens Note inspissated, jelly like secretion in lumen of seminal vesicle

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RETROPERITONEAL ECTOPIC SEMINAL VESICLE COMMUNICATING WITH A CONTRALATERAL SOLITARY KIDNEY REPORT OF A CASE

HENRY A AZAR AND SHELDON C SOMMERS

From the Laboratory of Pathology, Massachusetts Memorial Hospitals, Boston, Mass

In this paper is reported a case of agenesis of the left kidney and renal vessels with drainage of the lower calyx of the solitary right kidney into an ectopic left seminal vesicle located in the retroperitoneal space just above the sacrum This anomaly has apparently not previously been recorded However, it appears to be closely related to another rare congenital malformation of the genitourinary tract in which there is an extravesical ureter opening into the male seminal tract

CASE REPORT

J H (M M H 389255), a 30-year-old white male engineer, was known to have a right solitary kidney since the age of 21 He was first admitted to the Massachusetts Memorial Hospitals on January 3, 1952

In 1943, the patient had pyuria and x-ray examinations showed a single kidney on the right The pyuria cleared after sulfonamide therapy In 1951, a biopsy of the testes revealed normal spermatogenesis The patient was married but had no children There was a past history of asthma and hay fever The family history was unremarkable, and no congenital or familial diseases were recorded

On physical examination the patient appeared healthy and well developed The blood pressure was 110/60 The kidneys were not palpable The left testicle was smaller than the right Both vasa deferentia felt normal Rectal examination revealed a moderately enlarged prostate but the seminal vesicles were not felt The urine was clear and normal The blood urea nitrogen was 60 mg per cent on one occasion and 51 mg on another Cystoscopy revealed a markedly narrowed internal urethral sphincter The right ureteral orifice was normal, the left ureteral orifice was not visualized The contracted bladder neck was resected transurethrally and an adequate internal urethral orifice was obtained

The patient was re-admitted on February 1, 1957 because of a generalized erythematous eruption thought to be allergic in nature The blood pressure was 174/126 The urine contained clumps of white blood cells and cultures yielded Proteus spreader and enterococci Retrograde pyelography demonstrated dilatation of the right kidney pelvis, calyces and ureter On February 12, 1957, the patient underwent a right ureterostomy at which time a stricture at the right ureterovesical junction was corrected The postoperative course was complicated by pyuria, severe anemia and a transfusion reaction Shortly after the operation the right testicle became swollen, tender and warm A right orchiectomy was performed on March 22, 1957 Pathological examination of the specimen (S-57-

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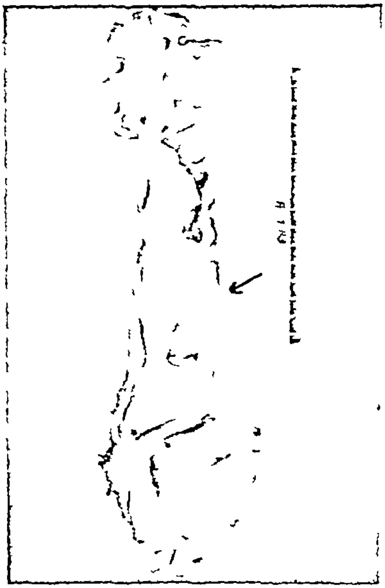

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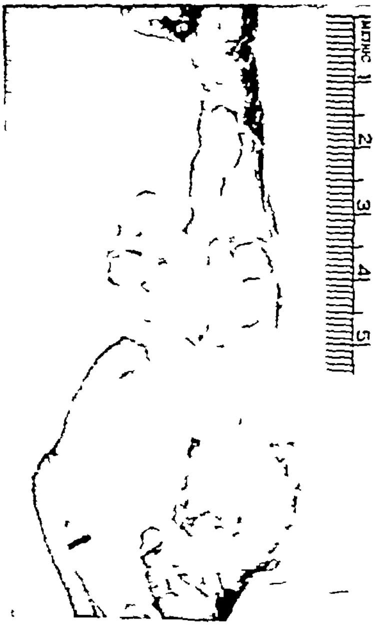

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apex The lungs weighed 830 gm together There was marked hyperemia at the bases and there was a considerable amount of white frothy fluid exuding from the cut surfaces of the lung parenchyma and within the bronchial tree All four parathyroid glands were moderately enlarged and the largest measured 0 8 by 0 6 by 0 4 cm There was slight osteoporosis of the skeleton

Microscopic examination In the right kidney there was considerable atrophy with a loss of normal architecture There was a diffuse chronic inflammatory reaction with fibrosis, scarring of the glomeruli and cystic dilatation of the convoluted tubules imitating the appearance of thyroid tissue There were numerous hyaline and granular casts in the collecting tubules The arterial and arteriolar walls showed moderate thickening, fibrosis and hyalinization (grade 2 arteriolosclerosis)

The duct connecting the lower calyx to the ectopic seminal vesicle was lined by a transitional type of urogenital epithelium, similar to that lining the renal pelvis and ureter The wall of the duct was the site of chronic inflammatory reaction The ectopic seminal vesicle was lined by one layer of columnar cells The muscular wall was well developed The lumen of the seminal vesicle was filled with an inspissated, granular and partly calcified secretion containing concretions, which was also present in the normally situated right seminal vesicle (fig 3) There were no aberrant renal structures observed in the vicinity of the ectopic seminal vesicle The prostate showed both acute and chronic inflammation The ejaculatory ducts were not identified The left testis showed slight peritubular fibrosis The Sertoli cells were abundant and there was marked depression of spermatogenesis The Leydig cells were likewise decreased in number The lumen of the left vas contained hyaline granules similar to those observed in both seminal vesicles

Pathologic diagnoses, aside from the urogenital anomaly and orchiectomy, included chronic pyelonephritis, arteriolosclerosis grade 2 with nephrosclerosis, cardiac hypertrophy, pulmonary congestion and edema, secondary parathyroid hyperplasia, renal osteitis, and clinical uremic state

DISCUSSION

Abnormal drainage of the ureter into the seminal tract has been occasionally diagnosed clinically and more often observed at autopsy In the 32 cases reviewed by Riba, Schmidlapp and Bosworth,[1] this anomaly was noted 21 times on the left and 11 times on the right The corresponding kidney was rudimentary in 14 cases, absent in 10, fibrosed in 2, cystic in 2, normal in one, and a double kidney was noted 3 times The ureters opened into the seminal vesicle in 22 instances (18 left, 4 right), and in the remaining cases into the vas deferens or ejaculatory duct (7 right, 3 left) Goldstein and Heller[2] reviewed 10 cases of ectopic ureter opening into the seminal vesicle, all diagnosed clinically In this group, the anomaly occurred 7 times on the left and 3 times on the right The corresponding

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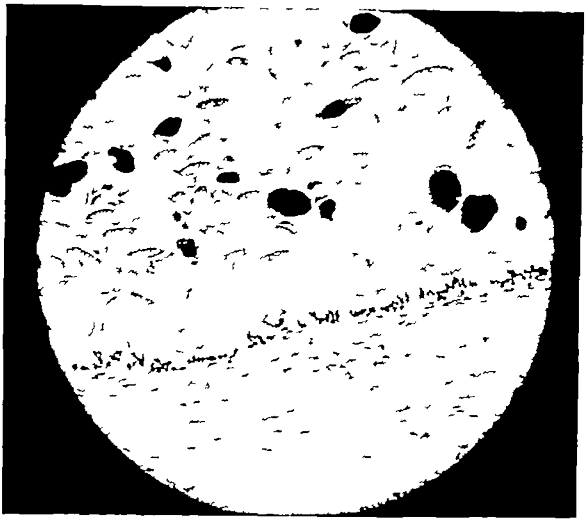

FIG 3 Section of wall of ectopic seminal vesicle showing smooth muscle, partly stratified columnar epithelium and hyaline and calcified granules in lumen H & E × 80

1128) showed slight decrease in spermatogenesis, slight chronic inflammation of the capsule, and chronic inflammation with serofibrinous exudation of the cord Subsequently, the patient went into progressive renal failure and died on August 8, 1957 in a state of uremia and pulmonary edema

Autopsy findings (A-57-119) The body was that of a well-developed adult male The external genitalia and hair distribution were normal

The major findings were limited to the genitourinary organs, heart, lungs and parathyroid glands

The right kidney was small, lobulated and weighed 70 gm The capsule stripped with difficulty The cortical surface was pale brown and finely granular The corticomedullary junction was indistinct and the entire thickness of the renal parenchyma averaged 1 5 cm The pelvis and calyces were moderately dilated The entire right ureter except for its distal portion was dilated and measured 1 5 cm in diameter The ureteral orifice was normal The lower pole of the right kidney gave rise to a duct-like structure which measured 7 cm in length This duct contained a lumen which communicated with the lower calyx of the right kidney and opened into a cystic left seminal vesicle located in the retroperitoneal space just above the sacrum (figs 1 and 2) The left kidney and ureter were not identified and there was no artery branching off the abdominal aorta opposite the right renal artery The left ureteral orifice was absent in the bladder

The right testicle had been previously excised The right seminal vesicle was normal in size and location, but no left seminal vesicle was present in the usual location The left testicle was located in the left scrotal sac and was grossly unremarkable The left vas deferens joined the ectopic seminal vesicle in the retroperitoneum The prostate was normal in size and shape

The heart was enlarged and weighed 480 gm The left ventricular wall was hypertrophied and measured 1 7 cm in thickness at its base and 1 0 cm at the apex The lungs weighed 830 gm together There was marked hyperemia at the bases and there was a considerable amount of white frothy fluid exuding from the cut surfaces of the lung parenchyma and within the bronchial tree All four parathyroid glands were moderately enlarged and the largest measured 0 8 by 0 6 by 0 4 cm There was slight osteoporosis of the skeleton

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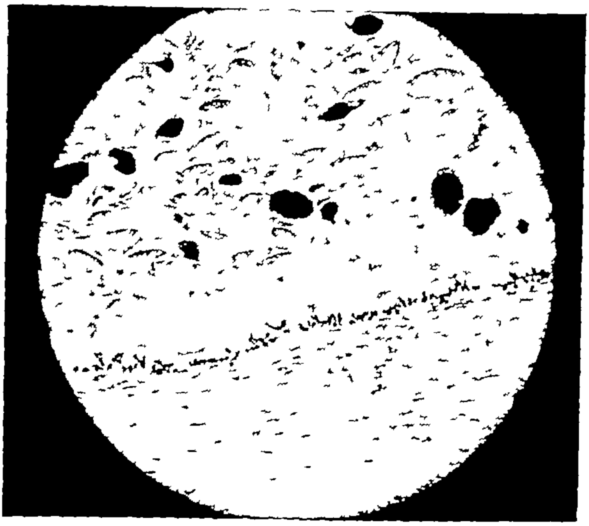

FIG 3 Section of wall of ectopic seminal vesicle showing smooth muscle, partly stratified columnar epithelium and hyaline and calcified granules in lumen H & E × 80

1128) showed slight decrease in spermatogenesis, slight chronic inflammation of the capsule, and chronic inflammation with serofibrinous exudation of the cord Subsequently, the patient went into progressive renal failure and died on August 8, 1957 in a state of uremia and pulmonary edema

Autopsy findings (A-57-119) The body was that of a well-developed adult male The external genitalia and hair distribution were normal

The major findings were limited to the genitourinary organs, heart, lungs and parathyroid glands

The right kidney was small, lobulated and weighed 70 gm The capsule stripped with difficulty The cortical surface was pale brown and finely granular The corticomedullary junction was indistinct and the entire thickness of the renal parenchyma averaged 1 5 cm The pelvis and calyces were moderately dilated The entire right ureter except for its distal portion was dilated and measured 1 5 cm in diameter The ureteral orifice was normal The lower pole of the right kidney gave rise to a duct-like structure which measured 7 cm in length This duct contained a lumen which communicated with the lower calyx of the right kidney and opened into a cystic left seminal vesicle located in the retroperitoneal space just above the sacrum (figs 1 and 2) The left kidney and ureter were not identified and there was no artery branching off the abdominal aorta opposite the right renal artery The left ureteral orifice was absent in the bladder

The right testicle had been previously excised The right seminal vesicle was normal in size and location, but no left seminal vesicle was present in the usual location The left testicle was located in the left scrotal sac and was grossly unremarkable The left vas deferens joined the ectopic seminal vesicle in the retroperitoneum The prostate was normal in size and shape

The heart was enlarged and weighed 480 gm The left ventricular wall was hypertrophied and measured 1 7 cm in thickness at its base and 1 0 cm at the

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MUMPS EPIDIDYMITIS

HOWARD E HARTMAN

Mumps "orchitis' occurs in approximately 18 per cent of adult males with epidemic parotitis from 2 to 14 days (usually 4 to 6) after onset of the parotitis While relatively ignored by most physicians, this usually represents an epididymo-orchitis as first brought out by Sorel[1] Candel[2] noted the involvement of both the testis and epididymis in at least 85 per cent of 78 cases studied

Primary onset of mumps epididymitis prior to orchitis has been observed in two cases This observation has been previously recorded some three times in the literature Candel[3] reports the occurrence of bilateral epididymitis preceding testicular involvement by 2 days, Waddelow,[4] 2 days, Feiling[5] a more involved course with a left epididymitis on February 12, parotitis February 14, submaxillary adenitis February 18 and orchitis when the parotid and submaxillary were subsiding Five cases[6-8] have been cited in the older literature in which only the epididymis was involved, however, these probably represent an error in terminology, i e Phillips[7] alludes to the epididymis, but he describes testicular involvement and Chauvin[8] describes two cases of pure epididymal involvement from a total of 19 cases which would appear to be most unusual from a statistical standpoint

CASE REPORTS

Case 1 G E B , Reg No 127281, a 35-year-old-white man, was admitted to the hospital May 13, 1956 with parotitis of 3 days' duration ACTH 20 mg b i d was instituted The patient was first seen by the author on May 14 He stated that on May 13 he had mild tenderness and swelling above the testicle proper on the right side, and that the swelling diminished after receiving the shots No urinary symptoms were present Physical examination after 14 hours of low dosage ACTH therapy Left scrotal contents normal, on the right side there was mild induration and tenderness of the head of the epididymis The testis itself was slightly smaller than the left with considerable softening It was nontender The spermatic cord and vas deferens were normal Prostatic examination was normal It was recommended that ACTH be continued On May 15 the epididymis was less tender, but the body of the epididymis also was involved in the process, and the patient's temperature was elevated On May 16—temperature was spiking, a slight increase in size of the right testis proper was noted for the first time Stilbestrol and aureomycin were administered On May

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[7] Phillips Lancet 1 23, 1911

[8] Chauvin Thesis 1900 cited by Feiling[5]

kidney was hypoplastic in 6 instances There was hydronephrosis in two patients and double kidney in two In 6 patients the kidney was nonfunctioning Sterility was ascertained in only two patients This developmental defect is ascribed to a failure of the wolffian duct and ureter to become separated in the urogenital segment of the cloaca during the fifth and sixth weeks of fetal life, thus resulting in abnormal communications between the ureter and the seminal tract, which is also derived from the wolffian duct [3] [4]

In the case presented here, there was an abnormal connection between the lower calyx of a solitary right kidney with a contralateral seminal vesicle which lay above the sacrum in the retroperitoneal space This "crossing" can be best explained by assuming that the solitary kidney represents an abortive double kidney or horseshoe kidney This is an exaggeration of the situation encountered when an ectopic ureter opens into a normally situated seminal vesicle Although the left testis was producing sperms, these apparently never reached the urethra and probably stagnated in the ectopic seminal vesicle It is assumed that the hyaline and partly calcified granules may represent aggregates of degenerating spermatozoa There is no evidence that the seminal fluid had reached the right renal pelvis

Ectopia of the seminal vesicle and its connection with the contralateral renal pelvis were not suspected clinically in this case Intravenous pyelography was contraindicated because of the allergic background of the patient and no seminal vesiculography was done

SUMMARY

A case of an adult male patient is presented with a solitary right kidney draining into an ectopic left seminal vesicle situated retroperitoneally just above the sacrum It is believed that this unique anomaly is an exaggeration of the situation with an ectopic ureter opening into a normally situated seminal vesicle

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[3] Campbell, M F Ectopic ureteral orifice Surg , Gynec & Obst , 64 22, 1937

[4] Culver, H Extravesical ureteral opening into the genital tract in a male Tr Am Assn Genito Urin Surg , 30 295, 1937

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TERATOMA OF THE EPIDIDYMIS A MATURE ADULT TYPE INCLUSION TUMOR OF THE EPIDIDYMIS IN AN 18-MONTH-OLD CHILD

ROBERT COWEN

Tumors of the testis and especially of its appendages are extremely rare under 2 years All tissue types have been reported, from embryonic pigmented ocular tissue in a retinoblastic teratoma of the epididymis[1] to a papillary cystadenoma [2]

Primary epididymal tumors are generally referred to as adenomatoid in a recent complete summary by Rankin [3] In reviewing 100 cases Wentzell[4] calls 70 per cent adenomatoid, the age group being 29 to 57, and the benign malignant ratio 74 to 26 In a report of the case of a 3-months-old child Robertson[5] states that only 4 per cent are benign The occurrence in the lower pole is four times that in the upper, and the left is twice as frequent as the right An adenomatoid tumor of the epididymis in the newborn reported by Rapoport and Morgan[6] places the age range as 15 to 78, most being in the fourth decade

Testicular adenomatoid tumors have been recorded in infants by Sakaguchi[7] and Golden and Ash[8] and Magner [9] Most recently in reporting teratoma of the testis in an infant, Meyer and Coughlin[10] have no evidence of any similar tumor in the epididymis Origin of epididymal tumor may be from the müllerian ducts, remnants of the appendix testis, or wolffian duct remnants of the appendix epididymis, or aberrant ducts of the paradidymis Wolffian duct remnants never show ciliated epithelium

Of the inclusion type tumors, teratoma is cystic, undifferentiated, and malignant, while the dermoid is hard, well differentiated, and benign

The following case of an inclusion type tumor with all dermal type of tissue of a mature teratoma of the epididymis, the residual testis being normal, is presented

R A , aged 18 months, born in Mexico, was admitted to the North Detroit General Hospital (No 40054) Examination disclosed a cystic, somewhat transilluminable left scrotal neoplasm, about 2 by 2 cm , discrete from the testicle No other abnormality was present except first degree hypospadias No steroid, nor other tests were made, and consent was obtained for removal of the growth without the testicle Diagnosis Cyst (multilocular) of the left epididymis

On April 30, 1957, epididymectomy was performed A moderate amount of hydrocele fluid was present in the tunica vaginalis, and a bluish cystic neoplasm

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17 the patient still had chills and fever, prostate and seminal vesicle remained nontender, the right testis was enlarged to approximately double its normal size, and tender, the epididymis was slightly smaller than previously with minimal tenderness Cortisone 100 mg a day was started By May 18 a decrease in size of the testis was noted By May 19 temperature had returned to normal By May 20, the testis had completely regressed to normal size On May 28 examination revealed that the testis was small, round, soft and very slightly tender The epididymis was normal

Case 2 W J S , a 32-year-old white male physician, was seen by the author a month following an acute episode He noted onset of mumps at 3 00 a m Friday morning, January 18, 1957, 17 days following exposure He instituted self-therapy of stilbestrol 15 mg on Saturday By Monday afternoon he noted the onset of epididymitis without testicular involvement By Tuesday the testicle was involved in addition to the epididymis This epididymo-orchitis continued to increase, and he took 80 units of ACTH Wednesday morning with partial relief By Thursday, however, the process had recurred and reached its maximum Thursday evening with the temperature 105F Resolutions then occurred He was up and about by Sunday and returned to work one week later Three to four weeks later the gonad had atrophied to approximately one-third its normal size, and tenderness persisted for two to three months

COMMENTS

Prior to case 1, ACTH had been previously used by the author, following report of Solem[9] in 1954 Dosage schedules were 80 i u ACTH o d for one to three days with excellent results Case 1 was maintained on 40 units ACTH per day in an attempt to delimit dosage requirements This was obviously inadequate as the patient's response with the shift to cortisone was immediate Subsequent cases treated with cortisone (100 mg per day for several days) showed excellent response

As an incidental note, subsequently a small (approximately a dozen) series of cases of primarily nonspecific epididymitis was treated with cortisone (75 to 100 mg per day for 3 to 5 days) in an attempt to gain insight into the etiology and treatment of this disorder These were cases in young men with no history of prior genitourinary disease, negative urinalysis, nontender prostate and seminal vesicles noted on physical examination with the onset of epididymitis usually following unusual physical exertion No observable beneficial effect was noted

CONCLUSION

The so-called "mumps orchitis" is, in the majority of cases, actually epididymo-orchitis Two cases of onset of the epididymal component prior to the testicular involvement are reported Incidental notations of the efficacy, in adequate dosage, of ACTH and cortisone in the treatment of mumps epididymo-orchitis and absence of response of nonspecific epididymitis to this therapy are made

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TRUE HERMAPHRODITE SIBLINGS

W. A. MILNER, W. B. GARLICK, A. J. FINK and A. A. STEIN

From the Departments of Urology and Pathology, Albany Hospital, Albany, N. Y.

In a classical treatise on genital anomalies Young laid the foundation of acceptable criteria for the diagnosis of true hermaphroditism. He stated it to be the presence in the same individual of both microscopic ovarian and testicular tissues. From the first acceptable report of Salen in 1909 to 1956 there have been recently collected and reviewed 68 proven cases. Undoubtedly this reported number reflects only a small part of the actual incidence.

To date there have been no reported instances of true hermaphroditism occurring in siblings. The recent examination of two brothers for treatment of genital anomalies who were proven to be true hermaphrodites is considered sufficiently rare and of potential etiological implication to geneticists working in this field to warrant publication. Hermaphroditism is most often suspected when there are combined genital aberrancies but it is not usually considered in the differential diagnosis of testicular nodules. The following case of the older sibling, however, is an example of a testicular nodule which proved to be an ovotestis.

CASE REPORTS

Case 1. G. B., a 13-year-old white boy, was admitted to the Albany Hospital on August 29, 1955 with an undescended left testis. Past history revealed a full term spontaneous delivery with normal feeding, scholastic and social development. He had measles, mumps and chicken pox in early childhood without sequelae. The patient was active in contact sports and considered to be masculine in gender and orientation. There was one older male sibling, age 17, considered to be normal and a 12-year-old brother and 5-year-old sister also without genital anomalies. A one-year-old brother, however, was stated to have a marked chordee, penoscrotal hypospadias and undescended right testicle.

Physical examination disclosed a tall, slender, well-developed youth with an early pubertal male hair escutcheon and android type pelvis. Slight breast enlargement was present. A small testis was palpable in the left inguinal canal but it was not possible to bring it down to the scrotum manually. The right testis was in the scrotum and presented a pea-sized nodule palpable on the upper pole. The penis was of normal size and presented a balanitic one degree hypospadias with a narrow scrotal raphe band extending to the base of the penile shaft. See figure 1.

The lower pole of the left testis was also biopsied. On rectal examination, the prostate gland was identified. The next day a left orchiopexy and hernia repair with the scrotal placement of a normal-appearing testis and epididymis were performed. Division of the rudimentary chordee was likewise accomplished. A right scrotal exploration then revealed a 2.5 by 1.5 by 1.5 cm. brown, abnormal

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Read at annual meeting of Northeastern Section of American Urological Association, Whiteface, N. Y., September 12-15, 1957.

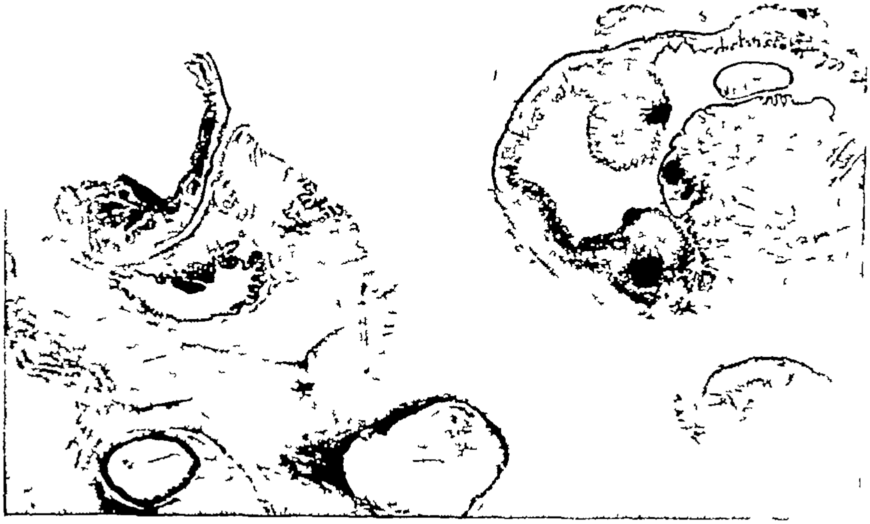


FIG 1

was easily separated from the fascial planes and removed with the epididymis in toto, leaving a very small, normal appearing testis

Pathological report (Dr John J Swihart) The gross specimen consisted of an irregular, lobulated mass weighing 2 gm and measuring 2 by 1 5 by 1 5 cm The mass appeared well encapsulated and was firm and gray tan in color Section disclosed whorls of tissue separated by linear cystic spaces At one portion two localized nodular areas each measuring 4 cm in diameter, were cystic with a thin wall and filled with dark brown material

Microscopic examination of the testicular tumor revealed an interesting arrangement of a number of kinds of tissue In one area typical epidermal cysts were surrounded by proliferating collagen with what were apparently a few adnexal skin masses Cylindromatous cells were present Areas of mucus-secreting cystic adenomas were seen with an accompanying lymphoid stroma In one area a considerable amount of clear cells was present characteristic of Brunner's glands In another area typical Paneth cells in association with gastrointestinal type mucosa were identified In still another area was what appeared to be respiratory mucosa with squamous metaplasia This represents a mature teratoma, and malignancy is not expected Diagnosis Teratoma of epididymis, mature (fig 1)

Teratoid tumor of the testicle regardless of histological character, is usually considered of malignant potentiality This tumor has many of the characteristics of the so-called adenomatoid tumor of epididymis, but is plainly a teratoma because of the large variety of cell types included In this particular case, it is difficult to believe that there is any malignant potentiality No tissue of feminizing character can be recognized

91 E Kirby, Detroit 2, Mich

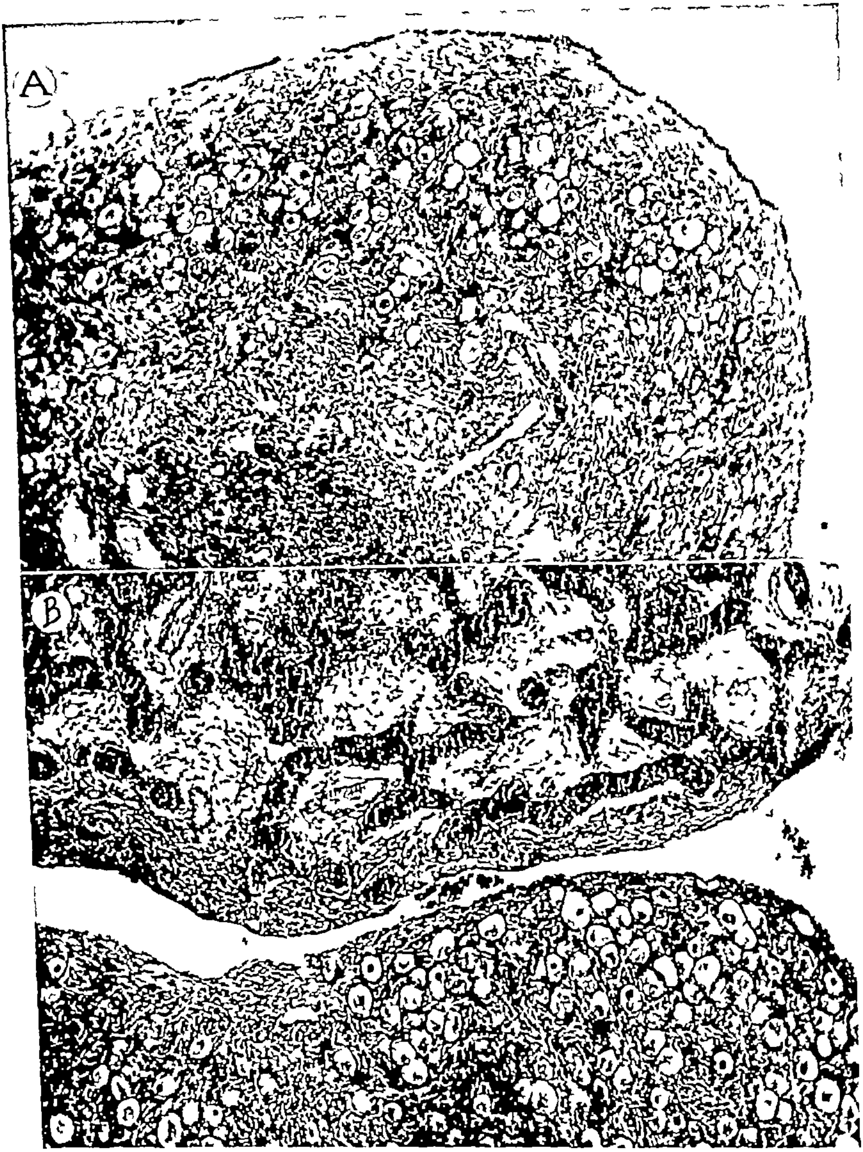


FIG 3 Case 2 *A*, nodule from upper pole of right testis composed of ovarian stroma with large numbers of ova × 120 *B*, nodule excised from upper pole of left testis showed both typical ovarian parenchyma and immature testicular tissue × 120

repair were done Upon opening the hydrocele sac, a very small nubbin of greyish-white tissue, measuring 0 2 cm in its greatest dimension, was excised from the upper pole of the normal-appearing right testis The histological report on the permanent section stated "ovarian tissue in which definite primordial follicles are numerous and characteristic ovarian stroma is present No testicular elements are present (fig 3, *A*) "

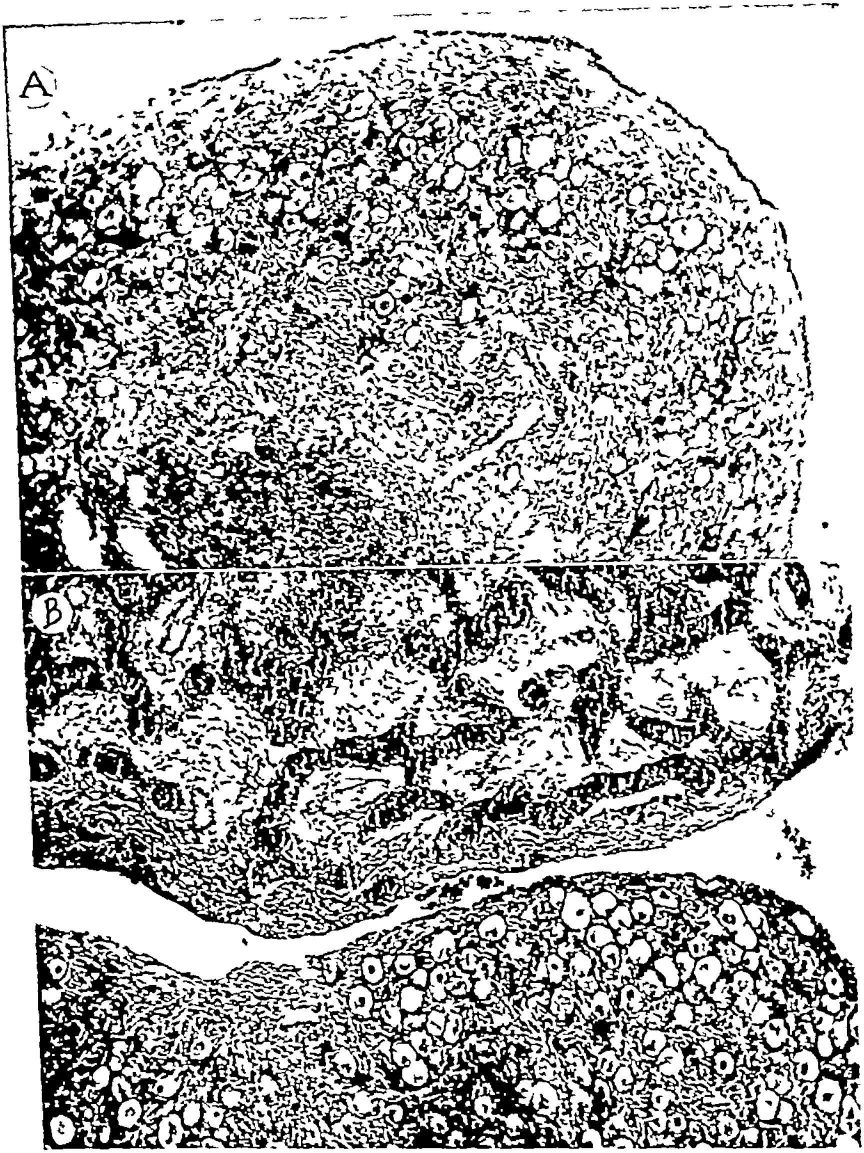
The need for further laboratory and surgical measures was stressed to the parents and with two instances of sexual aberrancy in the family they readily agreed *Laboratory measures were then performed and their results* were as follows F S H levels showed 16–64 mouse uterine units (normal 8–24 m u u), 17 ketosteroids of 8 2 mg per 24 hours, 17-hydroxy-corticosteroid level of 2 5 mg per 24 hours (normal 4–10 mg per 24 hours), pregnandial less than 1 mg per 24 hours (normal 5 trace amounts) and protein-bound-iodine showed 5 5 micrograms per cent (normal 4–10 mcg per cent)

On April 26, 1957, laparotomy and bilateral scrotal explorations were performed Examination of the pelvis did not reveal any female structures and exposure of each vas deferens to the internal inguinal ring was also normal The pelvic outlet was androgynoid The right gonad and spermatic cord were mobilized through a low inguinal incision This right greyish-white, smooth, ovoid gonad was then subject to bipolar biopsy and frozen section interpretation The upper pole revealed a focally sclerosed and inflamed epididymis The inferior pole showed testis displaying inactive spermatogenesis with *moderate* interstitial cell hyperplasia Attention was then directed to the left gonad which was exposed with its cord attachment through a similar incision The epididymis on the left was noted to be loosely attached to the testis, whereas the cord structures otherwise were normal-appearing on both sides The left gonad appeared rudimentary with a thin translucent-like tunica albuginea and slightly nodular in its superior pole *It was felt that the upper pole represented an ovarian segment of an* ovotestis On frozen section examination, this tissue was again reported as showing *inactive spermatogenesis and interstitial cell hyperplasia This finding* quickly led to biopsy of the lower pole and a report of ovarian tissue containing numerous ova and some follicular cysts (fig 2, *B*) A total excision of the left gonad was then performed

Convalescence was uneventful and the patient was discharged on metandren linguets 10 mg b i d with a final diagnosis of true hermaphroditism, bilateral type (i e , bilateral ovotestes)

Case 2 T G , a 13-month-old male child, was admitted on November 27, 1955, for correction of anomalous-appearing external genitalia Birth history revealed a full term, normal spontaneous delivery Other than frequent colds and measles at 5 months, there were no significant medical complaints or prior illnesses Interrogation of the mother indicated that there had not been any known gestational nutritional deficiency, medical illnesses or exposure to x-ray in either pregnancy Both parents stated they had no awareness of similar genital deformities in their respective families With the exception of the genitalia, the physical examination was within normal limits The scrotum was small and ill-defined and contained on the left a small, retractile testis On the right, there was, in addition to a palpable gonad, a communicating hydrocele and indirect inguinal hernia The penis was small with a severe chordee and a hypospadiac urethra existing at the penoscrotal angle

The next day, excision lysis of the chordee and transplantation of the urethra to the perineum were performed In addition, a right hydrocelectomy and hernia



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The patient, now 18 months old, was readmitted on June 11, 1956 Exploratory laparotomy the next day did not visualize the presence of any internal female sex organs Left high scrotal exploration mobilized a normal-appearing testis with a pearly-white tunica albuginea At the upper pole there was a palpable sensation of a nodule beneath the tunica The tunica was incised, expressing from the upper pole a small, firm, greyish-yellow, ovoid structure, measuring 0 8 by 0 4 by 0 4 cm , covered with a semitranslucent fibrous membrane This nodule was excised An additional biopsy from the bed of the excised nodule revealed the presence of junctional ovarian and testicular tissue (fig 3, *B*) Skin biopsy for sex chromatin pattern was negative (i e , male) Final diagnosis, in view of a proven ovotestis only on the left side, was true hermaphroditism, unilateral type It is considered probable that the remaining portion of the right gonad was testis and that this case also is representative of the bilateral type of true hermaphroditism Hypospadias repair is planned in a few years and androgen supplement will be used, if needed, at puberty or earlier

DISCUSSION

By definition, an ovotestis is the unilateral histologically proven presence of testicular and ovarian tissues occurring as a single mass or as adjacent anatomically separate nodules In our two cases of true hermaphroditism, it is likely that we have selectively enucleated the ovarian portion of the ovotestis Although McIver stated that only rarely can this be surgically accomplished, more recent studies indicate that bisexual gonad division is feasible and often surgically simple It is worth emphasizing that an estimated 80 per cent of the ovotestes in the reported cases of true hermaphroditism have lent themselves readily towards selective unisexual gonadal enucleation However, bipolar gonad biopsy and microscopic examination of all discrete nodules must be employed before removal, for gross interpretations frequently prove unreliable Actually not more than 20 per cent of ovotestes showed inseparable mixing of ovarian and testicular tissues, usually evidenced by juxtaposition blending or, rarely, a central core of of either ovarian or testicular substance

The association of the combination of hypospadias and cryptorchidism present in almost all the previously reported instances of true hermaphroditism was similarly noted in these two cases

Assembled under the entity of true hermaphroditism are congenital anomalies of the gonads and the primary sex characteristics These genitourinary anomalies are due to arrested or defective prenatal development Considerable controversy exists between geneticists and environmentalists as to the factors of major importance in the creation of this form of teratism That a persistent abnormal uterine environment was probably not responsible may be inferred from the fact that there were two normal siblings intermediate in age between these two cases The occurrence of two similar type (bilateral ovotestes) true hermaphrodites in the same family lends additional support to the hereditary concept of defective germ plasm

More vital in its implications have been the findings and beliefs of the environmentalists Most prominently, Jost has expounded on the ability of fetal gonadal hormones to produce the changes seen in hermaphroditism Also noted has been the hermaphroditic tendency of the retained genital ducts in vitamin A deficient rats during gestation The field of experimental teratogenesis has shed further light on this obtuse problem by implicating not only specific time periods in the life of the developing embryo when teratogenic stimuli may cause selective types of congenital anomalies, but also agent specificity wherein these stimuli, varying in quality and quantity, achieve the same anomalous result irrespective of time

SUMMARY

The first reported cases of true hermaphrodite siblings, bilateral type, have been presented

The presence of a testicular nodule combined with an external genital defect should suggest the diagnosis of true hermaphroditism and indicate the need for surgical exploration

Surgical sexual gonadal separation in the majority of ovotestes is feasible and histologically complete

The finding of true hermaphrodite siblings has given indirect support to the geneticists in their controversy concerning the etiology of this condition

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THE RATIONALE AND CURRENT STATUS OF DRUGS IN COMBINATION FOR URINARY INFECTIONS

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It would seem that a review of the rationale and present status of combined therapy would be of some value even though there are many unanswered questions The first era of antibiotics came with the narrow spectrum types, penicillin and streptomycin, and the second era with the so-called broad spectrum, first aureomycin, followed by chloromycetin, terramycin and the tetracyclines Now, as Finland[1] so aptly states, the trend toward the use of antibiotics in combination indicates that we are ushering in "the new antibiotic era, for better or for worse "

The incidence of the various bacteria varies with the clinical types of infection, such as uncomplicated or associated with other diseases of the urinary tract, and, to some extent, the postoperative group Also, age and sex may alter the incidence of a particular bacterium, for instance Escherichia coli is the leading pathogen in uncomplicated acute cystitis and pyelocystitis of women and children The cultures were all obtained from urinary tract infections from relatively broad sources which were my office practice, the out-patient urologic clinic of the University of Illinois (chiefly preoperative and postoperative patients), and the private practice of Dr Clay O Miller with both medical and surgical urologic patients However, our over-all incidence during the past year with over 250 positive cultures is about as follows Esch coli first, 50 per cent, Proteus and Enterococcus (Str fecalis) total 25 per cent, about equally divided, followed by Esch coli intermediate, paracolon, Pseudomonas, Aerobacter aerogenes, Klebsiella (friedlanderi), micrococci (variants aureus and albus), streptococci (pyogenes or viridans), each slightly under or over five per cent There were also numerous more rare species, each generally under one per cent There appears to be considerable geographical variation in the incidence of some organisms Kirby, Corpron and Tanner[2] have reported a high incidence of the Achromobacter group, a gram-negative bacillus, and they believed it was a largely hospital-acquired cross infection In my series, Achromobacter has not been found in more than one per cent of the cases Single genera requiring combined therapy most frequently are Proteus, Enterococcus, and Pseudomonas The presence of two or more offending bacteria is common, especially in chronic infections, and here more than one agent may be indicated

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Cycloserine (seromycin) and penicillin V (V cillin) were supplied through the courtesy of Dr R S Griffith of Eli Lilly & Company and the novobiocin (albamycin) through the courtesy of Dr James Dugger of the Upjohn Company

[1] Finland Maxwell Editorial Antibiotic Med & Clin Therapy 4 17 1957

Kirby, W M M , Corpron D O and Tanner D C Urinary tract infections caused by antibiotic resistant coliform bacilli J A M A 162 1, 1956

The first requirement for a successful result from combinations is sensitivity sufficient to inhibit the bacteria in the expected concentration of the drug in the urine and the tissues The pitfalls in the interpretation of sensitivity tests are tendencies to pay too much attention to intermediate or doubtful reports, such as slightly or partially sensitive, whereas highly sensitive or completely resistant are likely to correlate with the expected response in the presence of infection In my opinion, the use of more than two concentrations of discs only leads to confusion Intermediate readings are of value only for choosing drugs which are to be used in combinations When bacteria grow profusely during the administration of an antimicrobial agent in full dosage it will be found invariably that there is no inhibition of growth adjoining the disc on the inoculated agar and also no significant reduction of the pyuria, if present at the onset of therapy

There are some recent indications of controversy on the role of laboratory findings 1) Is there any correlation between the in vitro susceptibility tests and the clinical effectiveness of antibiotics? 2) Which are more frequently encountered, laboratory findings of susceptibility to antibiotics followed by clinical success, laboratory findings of susceptibility followed by clinical failure, laboratory findings of resistance followed by clinical failure? 3) Is it of economic advantage to the patient and/or the physician to avail themselves of laboratory facilities for the diagnosis and proper treatment of infections?

Also it would seem that too often sensitivity tests include bacteria of the urinary tract which seldom are pathogenic, such as alpha streptococci and the Micrococcus groups other than Staphylococcus (variant aureus) which is usually pathogenic Such reports may not only increase the cost but may also be misleading

The best documented reason for the use of two agents is infection where there are both bacillary and coccal organisms, and the best drug for one may not be the best for the other These infections often have failed previously of cure and, if static, there is ample time for sensitivity tests to aid in the selection of two or more medicaments In general, it would seem better to prescribe singly rather than the packaged combinations The latter may be more convenient for the patient, but there is temptation to prescribe them on the basis of trial and error Parenteral administration when indicated has advantage, such as combined penicillin and streptomycin in a single injection

The delay or prevention of emergence of resistant organisms should be an important reason for the administration of drugs in combination It must be known which combinations and which organisms will respond consistently The classic proven example of such delay is the use of PAS (paraminosalicylic acid), isoniazid and streptomycin in tuberculosis infections As yet there is no substantial proof that such prevention can occur with other bacteria of the urinary tract, and its ultimate value has yet to be proved

There seems to be general agreement that the incidence of side reactions is proportional to the dosage and duration of therapy In general, a lower dosage of either agent used in combination would be expected to produce fewer reactions For instance, when novobiocin is given in dosages of one gram per day for longer than five or six days there will be more than ten per cent dermatologic reactions Recently we have given this drug in dosages of 0 5 gm per day combined with other agents in half dosage without any side reactions even though novobiocin had been administered in the latter dosage from two to four weeks Of course, it is possible that patients are being subjected to the added risk of development of sensitivity or if already sensitive to one or the other drugs it may not be clear to which of the two drugs the reaction is due

There has been considerable interest recently in synergism or the potentiating effect of two drugs used concurrently so that there is a greater antibacterial action than the additive effect of two agents that are not synergistic It is generally accepted that the results are superior when streptomycin and penicillin are given concurrently, especially against Enterococcus (Str faecalis) than if double the dosage of each is used singly In vitro it has been demonstrated that some bacteria of the urinary tract result in wider zones of inhibition in sensitivity tests when two agents are combined in one disc, each in half the concentration as compared to the single disc of one in full concentration However, it is difficult to evaluate such combinations in vivo, chiefly for lack of suitable controls It would seem that more observations are required before specific combinations can be said to be synergistic *in vivo for a particular genus of offending* bacteria

Clapper and Sun[3] reported a synergistic action in vitro against 36 per cent of Pseudomonas when polymyxin was combined with tetracycline and 80 per cent when polymyxin in low concentration was combined with chloromycetin They also noted synergism with some strains of Proteus and with Str faecalis using penicillin plus chloromycetin, streptomycin plus novobiocin or penicillin plus streptomycin Clapper, Sun and Meade[4] state that furadantin and chloromycetin were synergistic against nearly all strains of Aerobacter aerogenes, Proteus species and Str faecalis tested in concentrations readily obtainable in the urine

It is significant that the above investigators found penicillin when used in combination in vitro to inhibit the growth of the genus Proteus Recently Holloway and Scott[5] cured a Proteus mirabilis bacteremia with large doses of penicillin (12 million units per day) Apparently up to 50 per cent of Proteus may be sufficiently sensitive in vitro to warrant a trial with large doses of penicillin alone or in combination with other anti-Proteus drugs I have used penicillin V in combination with other agents with encouraging results but I now believe insufficient penicillin was used at the time

Another reason for giving drugs in combination is to prevent the emergence of undesirable flora in the intestinal tract This is likely to occur during administration of some of the antibiotics, notably the broad spectrum type It has been said that when tetracycline is combined with nystatin Monilia emerge less frequently The emergence of virulent Staphylococcus (variant aureus) may at times replace the normal flora and produce an acute enterocolitis However, if this disease is recognized promptly it is not a problem since it will generally respond to anticoccal therapy and for this purpose erythromycin has been used more extensively If the Staphylococcus is found to be resistant to erythromycin there are other anticoccal agents of value, such as novobiocin and possibly oleandomycin (matromycin) The exact value of the combination of tetracycline and anticoccal agents to prevent the emergence of virulent cocci has not as yet been determined Apparently there is no harm in such combination and, as stated above, it does have an indication for administration in mixed coccal and bacillary infections

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[3] Clapper, W E and Sun C The in vitro effect of combinations of antibiotics on resistant strains of bacteria commonly found in urinary tract infections Antibiotics & Chemotherapy 7 75 1957

[4] Clapper, W E Sun, C and Meade, G H The combined activity of nitrofurantoin and antibiotics on strains of resistant bacteria commonly found in urinary tract infections Antibiotics & Chemotherapy, 7 193, 1957

[5] Holloway W J and Scott E G Proteus bacteremia treated with large doses of penicillin Antibiotic Med & Clinical Therapy 4 104, 1957

It has been stated that antagonism may occur in certain instances, particularly when two drugs are given in low dosage Therefore, the effectiveness is less than if either one were administered alone in full dosage However, it is difficult to determine how frequently this happens in vivo and it is also not clear which combinations are most likely to act in this way

It would seem that outside of the mixed bacillary coccal infections and other reasons not so clearly defined for the use of combinations there are outstanding three resistant species where combined therapy is frequently needed However, the first premise required before the use of two drugs is that each bacterium be proved to be sensitive to one or both drugs In the past concurrent administration of streptomycin and chloromycetin was the most effective against the genus Proteus Enterococcus (Str faecalis) responds well to the combination of streptomycin and penicillin, but if the Enterococcus is resistant to penicillin, erythromycin can well be substituted For the third resistant genus—Pseudomonas—a combination of streptomycin and tetracycline is still a good combination but the more dangerous polymyxin may be indicated in very severe infections where it may serve as a life-saving measure The incidence of Pseudomonas in urinary infections is much less than Proteus and Enterococcus

It may be that we are entering a fourth era of antimicrobial therapy in which efforts will be made to increase host resistance This may increase the effectiveness of an antimicrobial drug provided that the specific bacterium is known to be sensitive to it Such potentiating antibiotic activity could concern both specific and nonspecific immune substances For instance, Waisbren[6] has recently reported that the combination of antibiotics and gamma globulin may give a clinical result that could not be obtained with the antibiotics alone No doubt measures for the purpose of increasing host resistance will be explored further There is some consideration being given at the present time to the possibility that properdin, a newly described serum protein, is a factor in host resistance Properdin may prove to be a valuable tool to measure attempts to increase host resistance, both specific and nonspecific

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[6] Waisbren B A The treatment of bacterial infections with the combination of antibiotics and gamma globulin Antibiotics & Chemotherapy, 7 322, 1957

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CLINICAL AND LABORATORY OBSERVATIONS OF SULFAMETHOXYPYRIDAZINE (KYNEX) IN URINARY INFECTIONS

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Favorable results have been reported through the use of kynex for infections of the urinary tract by Frisk and Wassen[1] and also by Boyer, Strickland and Gylfe[2] Kynex (sulfamethoxypyridazine) is of interest because of its long-acting effect associated with a high serum concentration on comparatively small dosage Our series consisted of 50 patients, 20 of whom had pyuria grossly, and 30 typical chronic nonspecific prostatitis in whom generally the second glass of urine was clear and microscopically normal Not included in this report are other patients who have not had sufficient follow-up to be included, and in addition a few patients to whom kynex has been administered in combination with other drugs

About half of the patients with pyuria had acute infections and responded favorably to kynex, as would be expected with other sulfonamides in higher dosage, although a few of these patients in the early part of our study were given 2 gm kynex daily instead of the current dosage of 1 gm The infections were chronic in the other 10 patients many of whom had Proteus or Pseudomonas which had previously failed of cure on other sulfonamides as well as antibiotics They also failed of cure on kynex Many of these patients had associated disease of the urinary tract, such as carcinoma of the prostate, either before or after resection, or inoperable calculi We were chiefly interested in the evaluation of kynex in chronic nonspecific prostatitis since it is known to have a higher serum and tissue concentration than other sulfonamides in like dosage In all cases cultures were made and the organisms identified before and during therapy and, with few exceptions, after a suitable period following the discontinuance of the drug In most cases when the cultures revealed gram-negative bacilli mixed with other flora, generally gram-positive, the bacilli were eliminated with the exception of Proteus and Pseudomonas In a majority of patients cultures of the prostatic secretion did not yield a growth during the administration of kynex but the gram-positive organisms generally emerged following discontinuance of medication However, in some patients the prostatic secretion became free of pus, notably in those who had coliform bacilli prior to the institution of kynex

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Kynex was supplied through the courtesy of Lederle Laboratories Division American Cyanamide Company
Read at annual meeting of North Central Section of American Urological Association Mackinac Island, Michigan, August 29–31, 1957

[1] Frisk, A R and Wassen A Clinical evaluation of sulfamethoxypyridazine Antibiotics Annual, 1956–1957, p 424

[2] Boyer, W P Strickland, C S and Gylfe, J M Sulfamethoxypyridazine (kynex) a new long acting sulfonamide Antibiotic Med & Clin Therap, 3 378, 1956

It is generally accepted that the sulfonamides exert antibacterial effect by interfering with the normal metabolism of the bacterial cells and the primary action is one of bacteriostasis This eventually leads to bactericidal effects It is probable that in simple acute uncomplicated cystitis and pyelitis the higher concentration of sulfonamides in the urine has not been actually needed since the bacterial population may be relatively small This applies especially to acute infections due to Escherichia coli On the other hand, in chronic infections often associated with urinary stasis the bacterial population may be so large that none of the sulfonamides will be effective in safe dosage

Nichols and Finland[3] have recently reported that "the administration of 1 0 gm every 48 hours in patients produced average plasma levels ranging between 5 and 12 5 mg of total sulfamethoxypyridazine per 100 ml and also significant concentrations in their urine in the intervals between doses " Therefore, since such levels can be obtained with an average of 0 5 gm per day it would seem to be an ideal sulfonamide to combine with other antibacterial agents There is apparently some value in such combinations since sulfonamides are now available combined with penicillin, erythromycin or tetracycline We have used kynex with other drugs, most commonly with cycloserine (seromycin) This method of administration should be explored further

We have been fortunate in having a very low incidence of toxic manifestations There has been only one known instance of a generalized skin eruption, associated with fever, which occurred on the sixth day of therapy and this happened early in our observations when patients were being given 2 gm of kynex per day In spite of its known delayed excretion the reaction cleared up in a period about as usual as for other sulfonamides An antihistamine was administered immediately after the onset of the reaction and may have aided its control Another patient reported erythema over his abdomen which disappeared in 24 hours without discontinuance of kynex A few patients complained of intermittent headache or mild gastrointestinal discomfort but generally not sufficient to require discontinuance of the drug Many patients on dosages of one gram or less daily have taken kynex up to one month without any demonstrable toxicity

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[3] Nichols, R L and Finland, M Absorption and excretion of sulfamethoxypyridazine J Lab & Clin Med , 49 410–421, 1957

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SPECIES OF THE GENUS PROTEUS AND SOME UROLOGICAL IMPLICATIONS

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We have been impressed during the past few years with the increasing incidence of Proteus mirabilis as compared with other Proteus species Many recent text books as well as published articles do not give the relative incidence of these organisms in urinary tract infections However, Flippin and Eisenberg[1] in Philadelphia reported the different species encountered were P mirabilis 38 per cent, P vulgaris 30 per cent, P rettgeri 21 per cent, and P morganii 11 per cent They also state that only the strains of P vulgaris and P morganii show a significant susceptibility to antibiotics Stewart and Rowe,[2] Los Angeles, identified 100 consecutive gram-negative bacilli They found that 20 per cent of these, predominantly from infections in children, were Proteus species There was only a slight difference in the incidence of the four species of Proteus reported in their study

First, our observations concerned the incidence of the spreading Proteus mirabilis and vulgaris, and after 25 such cultures we identified all gram-negative bacilli with the exception of Pseudomonas strains in order to determine the incidence of the non-spreading Proteus rettgeri and morganii Of 150 such non-spreading gram-negative bacilli two were P morganii and five were P rettgeri Of the 79 spreading Proteus organisms identified 73 were P mirabilis and six were P vulgaris The method as described by Schaub and Foley[3] was followed in the differentiation of the various species The cultures were all obtained from urinary tract infections from relatively broad sources which were the private practice of one of us (RDH), the out-patient urologic clinic of the University of Illinois (chiefly preoperative and postoperative patients), and the private practice of Dr Clay O Miller with both medical and surgical urologic patients Occasionally when cultures are made during antimicrobial therapy P mirabilis and P vulgaris were slow to spread (taking up to two or three days) and rarely required subculture, at least on the medium which was routinely used for the primary inoculations (Difco Nutrient Proteose No 3 Agar)

It is interesting to note that Hoyt, Seltzer and Pickett[4] in their speciation of 104 strains of Proteus isolated in the routine study of stool and urine specimens

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Read at annual meeting of North Central Section of American Urological Association, Mackinac Island, Michigan, August 29-31, 1957

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[1] Flippin, H F , and Eisenberg G M Antimicrobial Therapy in Medical Practice Philadelphia F A Davis Co , 1955, p 127

[2] Stewart, B L and Rowe, H J Nitrofuradantoin (furadantin) in treatment of urinary infections J A M A **160** 1221-1223 1956

[3] Schaub, I G and Foley, M K Diagnostic Bacteriology, 4th ed St Louis C V Mosby Co , 1952

[4] Hoyt, R E , Seltzer, M and Pickett, M J Rapid speciation of genus Proteus J Urol , **76** 292, 1956

reported the following incidence P vulgaris 11, P mirabilis 67, P rettgeri 5, and P morganii 21 They did not state the relative numbers of cultures from each of the two sources Again P mirabilis predominates over P vulgaris

There are several important urological implications in connection with this work Whether the increase of Proteus in urinary infections is associated with the ascending or the hematogenous route is not certain, but it seems most likely to be the former The high incidence of P mirabilis as compared with the other types would seem to indicate that sensitivity tests are more important than identifying the Proteus species since more than 80 per cent of those identified were P mirabilis It has been stated that P vulgaris is sensitive to novobiocin but this species is comparatively rare We have no data on the relative sensitivity of the various strains However, we are impressed with the increased incidence of P mirabilis to other gram-negative bacilli, being second in incidence to Escherichia coli in our series It is generally conceded that there is great difficulty in the eradication of this organism with antimicrobial agents, used singly or in combination

It would seem logical that infections in women are ascending and it is well recognized that they are increasingly more common in men following instrumentation and/or surgery As previously reported by one of us (RDH)[5] there has been a sufficient incidence of concurrent infections in husband and wife to indicate that there may be at times cross infection, as well known to occur in Trichomonas infestation One must consider that this could possibly occur with other bacterial infections of the urinary tract and suggests that in the presence of recurrent infections both husband and wife be examined for like bacteria

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[5] Herrold, R D The story of antimicrobial agents for urinary infections and some new concepts J Urol , 75 892–900 1956

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GANTRIMYCIN EFFECTIVE COMBINED THERAPY OF URINARY INFECTIONS

JAMES H SEMANS AND JAMES F GLENN

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The systemic therapy of genitourinary infections has received great emphasis in the literature in the past 30 years The introduction of effective chemotherapeutic agents occasioned great interest in this subject,[1] and this was subsequently followed by the introduction of the sulfonamide family of drugs in the treatment of urinary tract infections [2] More recently, of course, a host of antibiotics have been introduced which have varying degrees of efficacy in different types of urinary infection Most recently, it has been suggested that combined therapy of certain infections may prove more effective than any single form of treatment alone [3] Various combinations of chemotherapeutic agents, sulfonamides, and antibiotics have been employed by a number of investigators in an effort to determine the possible benefit of combination therapy [4-7] This method of treatment has been termed the synergistic approach to therapy

It is the purpose of this paper to introduce a new agent, gantrimycin, combining sulfisoxazole* (3,4-dimethyl-5-sulfanilamide-isoxazole) and oleandomycin, two proven effective agents, for the treatment of urinary tract infection The work presented in this paper represents a pilot study in the use of this new combination of a sulfonamide with an antibiotic The results of this introductory study of this new combined drug indicate that it has a definite place in the armamentarium of the physician treating urinary infection In brief, 52 per cent of patients treated in this series with gantrimycin were considered to show an excellent response Additional patients showed gratifying improvement, and in only a few instances was the trial therapy considered a complete failure It is of further interest that gantrimycin proved most effective against gram-positive organisms, effecting a success rate of approximately 80 per cent in such infections

GANTRIMYCIN

Gantrimycin is a new combined drug consisting of sulfisoxazole (gantrisin) and a new antibiotic, oleandomycin In the tablet form of the drug utilized in

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This study was carried out under a grant by Hoffmann LaRoche Incorporated, manufacturers of gantrimycin

[1] Alyea, E P and Roberts L C Chemotherapy in nonspecific *infections of urinary tract* J A M A , **115** 1345, 1940

[2] Hill, J H Comparative in vitro action of sulfanilamide, sulfapyridine and sulfathiazole in urine J Urol , **43** 491, 1940

[3] Jawetz, E Antibiotic synergism and antagonism Arch Int Med , **90** 301 1952

[4] Rhoads P S , Billings C E and O'Conor, V J Antibacterial management of urinary tract infections J A M A **148** 165 1952

[5] Rhoads, P S Management of urinary tract infections Post Grad Med , **21** 563, 1957

[6] Waisbren B A Treatment of bacterial infections with combination of antibiotics and gamma globulin Antibiotics and Chemotherapy , 7 322, 1957

[7] Winton, S S and Cheserow, E Clinical study of combined chemotherapy Tetracycline and oleandomycin Antibiotics Annual, 1956–1957 pp 55–62

* Gantrisin®

this study, the ratio was approximately five parts gantrisin to one part oleandomycin

Gantrisin of course, is familiar, having been in clinical use for a number of years[8] It is sulfisoxazole and its wide clinical usefulness is well known It has been proven effective in urinary infections with both gram-positive and gram-negative micro-organisms It is excreted in the urine in high concentrations as previously shown

Oleandomycin is a new antibiotic agent which is obtained from a strain of streptomyces antibioticus[9, 10] Its phosphated form has been proven to be quite stable and unaffected by gastric and intestinal secretions Oleandomycin is also excreted in the urine in relatively high concentrations In contrast with some of the older antibiotic agents, it is well tolerated in high dosage Extensive laboratory study has shown that oleandomycin exhibits a range of antibacterial activity similar to that of penicillin and erythromycin[7] Its effect is most marked against gram-positive micro-organisms, particularly staphylococci and streptococci

Because of the fact that gantrisin alone does not always prove satisfactory in the treatment of virulent gram-positive urinary infections, the combination of gantrisin and oleandomycin has been introduced in an effort to provide more complete therapy in such cases The combination utilized clinically in this study consisted of gantrisin 333 mg and oleandomycin 75 mg, in each oral tablet Dosage varied from two to five tablets given four times daily with approximately 90 per cent of patients in this series receiving the maximal dosage of five tablets four times daily The period of therapy varied from three to fourteen days, again with approximately 90 per cent of patients in this series undergoing treatment for a period of seven days

METHODS OF STUDY

The methods of study utilized here were fairly standard in the study of therapy of urinary infection Urinalysis with smear for bacteria was utilized to determine the presence of infection Urine culture and sensitivity studies were obtained at the time of initial examination, and therapy was instituted The patients were followed at appropriate intervals with followup urinalyses and smears Blood, serum and urine levels were obtained for both gantrisin and oleandomycin Finally tube sensitivity tests were accomplished to determine the relative efficacy of the combined drug

Determination of gantrisin levels was accomplished colorimetrically on blood, serum and urine samples at intervals of one hour to seven days subsequent to last oral dosage

Oleandomycin levels were determined by a two-fold serial dilution method utilizing brain-heart-infusion broth A standard test micro-organism, Strepto-

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[8] Price P C and Hansen A E Blood levels in relation to dosage of gantrisin in children with clinical observations Texas Reports on Biol and Med 9 764 1951

[9] Ross S PA 105 a new antibiotic Some clinical observations Antibiotics Annual 1955–56 pp 600–603

[10] Sobin B A English A R and Celmer W D PA 105 a new antibiotic Antibiotics Annual 1954–55 pp 827–830

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It is the purpose of this paper to introduce a new agent, gantrimycin, combining sulfisoxazole* (3,4-dimethyl-5-sulfanilamide-isoxazole) and oleandomycin, two proven effective agents, for the treatment of urinary tract infection The work presented in this paper represents a pilot study in the use of this new combination of a sulfonamide with an antibiotic The results of this introductory study of this new combined drug indicate that it has a definite place in the armamentarium of the physician treating urinary infection In brief, 52 per cent of patients treated in this series with gantrimycin were considered to show an excellent response Additional patients showed gratifying improvement, and in only a few instances was the trial therapy considered a complete failure It is of further interest that gantrimycin proved most effective against gram-positive organisms, effecting a success rate of approximately 80 per cent in such infections

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[6] Waisbren, B A Treatment of bacterial infections with combination of antibiotics and gamma globulin Antibiotics and Chemotherapy, 7 322, 1957

[7] Winton S S and Cheserow, E Clinical study of combined chemotherapy Tetracycline and oleandomycin Antibiotics Annual, 1956–1957, pp 55–62

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TABLE 2 *Organisms encountered*

Organism	Number of Cases	Lost to Follow up	Good Response	Poor Response	
				Complicated	Uncomplicated
Klebsiella aerobacter	15	1	4	2	8
Proteus morgagnii	5		2	1	2
Escherichia coli	24	1	16	1	6
Micrococcus albus	10		9	1	
Pyocyaneus	4			2	2
Anaerobic streptococcus	2		2		
Beta hemolytic streptococcus	1				1
Escherichia freundii	1				1
Gamma streptococcus	1				1
	63	2	33 or 52%	7	21
				28 or 44%	

five tablets of gantrimycin four times daily At the end of one week of therapy patients were re-examined, blood and urine levels of drugs were obtained, and followup urinalysis was accomplished A urinary smear negative for bacteria was established as the initial criterion of improvement In the absence of bacteria at the end of one week of therapy, gantrimycin therapy was discontinued The patients were seen again at the end of an additional week, at which time a final urine culture was obtained If, at this time, the patients' urine proved sterile, therapy was considered a success In addition, a number of patients were seen two to three weeks later and in each instance of previously recorded success there had been no evidence of recurrence

In this series, 48 per cent of patients did not meet the criteria established for a good response to therapy Of these, however, approximately one-half exhibited definite clinical improvement during the course of therapy Some few of these patients exhibited a change in the infecting organism by culture Patients who became asymptomatic on gantrimycin therapy, though the urine did not become sterile, were rated as clinically improved, there were sixteen such patients in this series, or approximately 25 per cent, showing clinical improvement without sterilization of the urine by laboratory tests

Absorption and excretion studies of gantrimycin were accomplished by the methods of measurement described above The results of these studies are shown graphically in figure 1, a multiple scatter-graph showing gantrisin levels in blood, serum and urine, and oleandomycin levels in serum and urine It is interesting to note that the peak levels of absorption and excretion of both gantrisin and oleandomycin were recorded at two to three hours following oral administration of the drug That the levels attained were effective in vivo and in vitro is attested by the clinical and laboratory improvement of the patients in the series and by tube sensitivity and inhibition studies which accompanied the determination of drug levels coccus pyogenes ATCC 8668, was used as the test organism Similar biologic assay was accomplished in both blood and urine samples

In vitro observation of the bacterial spectrum of gantrimycin suggested that gantrisin and oleandomycin were complementary Initial tube sensitivity studies suggested that a synergism between the two agents existed

RESULTS

Approximately one-hundred patients were treated in this pilot study These patients were drawn from those seen in the urology out-patient clinic at Duke Hospital and from the in-patient urology services of both Duke Hospital and the Veterans Administration Hospital, Durham, North Carolina In a number of these patients, the clinical and laboratory data obtained were deemed insufficient for inclusion in this series Sixty-three patients in whom data are sufficiently complete are included here A wide variety of urinary infections was encountered in this series as indicated in table 1 In general, patients having infection with known complicating factors of long standing were excluded from this series, though among those treated were patients with known urinary calculi, diabetes mellitus, neurogenic bladder, strictures, and, in one instance, carcinoma of the bladder Response to therapy was most gratifying in those patients with acute uncomplicated infections Over all, a 52 per cent success rate was recorded in the use of gantrimycin in urinary tract infections

A wide variety of infectious agents were also encountered in this study as shown in table 2 It will be noted here that the best response was obtained in the gram-positive group of organisms and the poorest response among the gram-negative micro-organisms The one exception to this statement is the rather gratifying response of E coli infections to treatment with gantrimycin Among this latter group of infections were three instances of hemorrhagic E coli cystitis which responded promptly and dramatically to brief periods of therapy with gantrimycin

Rigid standards were established for determination of a good response to therapy Generally, patients were treated for one week with maximal dosage of

TABLE 1 *Types of infection encountered*

Disease	Number of Cases	Lost to Follow up	Good Response	Poor Response
Pyelonephritis, chronic	9		1	8
Pyelonephritis, acute	5		3	2
Cystitis, acute	10		9	1
Cystitis, hemorrhagic	3		3	
Cystitis, chronic	9	1	1	7
Trigonitis urethritis, chronic	11		5	6
Prostatitis, chronic	6	1	2	3
Trigonitis urethritis, acute	8		7	1
Prostatitis, acute	2		2	
	63	2	33	28

tinued before this can be evaluated effectively Combined therapy of infectious disease has received strong criticism from some quarters[11] It is our impression that the use of two proven agents such as gantrisin and oleandomycin has a definite place in the therapy of urinary infections particularly those caused by the gram-positive micro-organisms This study does not indicate that gantrimycin is a broad spectrum agent to be used to the exclusion of other efficacious drugs[1, 2, 4] However our preliminary results lead us to the impression that it is an effective and valuable drug in the treatment of selected cases of urinary tract infection

SUMMARY

The results of a pilot study in the therapy of urinary tract infections with gantrimycin a combined drug consisting of gantrisin and oleandomycin, are presented An excellent response to therapy in a wide variety of urinary infections was obtained in 52 per cent of 63 patients studied Laboratory determinations of organism sensitivity and blood serum and urine levels of gantrisin and oleandomycin were accomplished Synergism between gantrisin and oleandomycin is suggested by this study though further study is indicated It is felt that gantrimycin offers effective therapy in selected cases of urinary infection particularly those involving the gram-positive micro-organisms

The authors wish to express their thanks to Dr Earl Haltiwanger and Dr J L Williams Jr who supervised the clinical studies presented and to Miss Mary Poston Mr Leo B Daniels and Miss Mary Todt of Duke Hospital for the bacteriological and chemical studies

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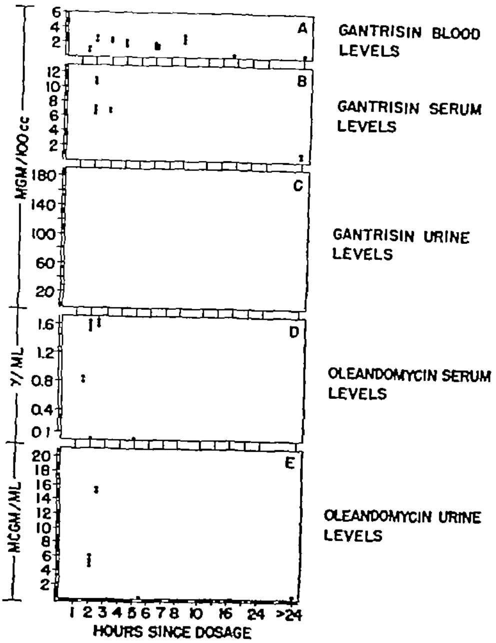

FIG 1 A series of graphs showing quantitative determination of levels of gantrisin and oleandomycin (gantrimycin) in serum, whole blood and urine

Tube sensitivity studies were carried out in eight patients, and indicate that synergism between gantrisin and oleandomycin may exist in the treatment of gram-positive urinary infections Further extensive work is indicated in this investigation

SIDE REACTIONS

Clinically, the patients included in this series were questioned and studied carefully for evidence of side reactions, and in only three patients were such reactions noted to a significant degree A few patients in the series exhibited mild nausea, and one patient developed vomiting after only one day of therapy, needless to say, the drug was discontinued at that point One additional patient developed rather severe diarrhea after three days on the drug, and the drug was discontinued after four days, this patient, however, is classified as a good response in this series since the urine cultures reverted to negative during the course of treatment and remained so one week following cessation of treatment A third patient developed a severe exacerbation of vaginal moniliasis after two weeks' therapy with gantrimycin in maximal dosage of five tablets four times daily We were thus impressed with the relatively small number of serious side reactions

DISCUSSION

This work represents only a pilot study in the use of the combined drug, gantrimycin, and further extensive clinical and laboratory study is indicated Synergism, a phenomenon which can be demonstrated only in the laboratory, is suggested by our study, but extensive experience with the drug must be ob-

TABLE 1 Status of bladder in patients without tidal drainage

Vertebral Levels	LMN						UMN						Mixed			Number of Patients
	Complete			Incomplete			Complete			Incomplete						
	Sp	Bl	TUR	Sp	Bl	TUR	Sp	Bl	TUR	Sp	Bl	TUR	Sp	Bl	TUR	
Cervical							9	1	2	17	3	4				36
Th 1-4							3			2						5
Th 5-8							4	2	1	2	1	1				11
Th 9-12	1						10	3	1	4	1					20
Lumbar	2			4	1		3			1			1			12
	3			4	1		29	6	4	26	5	5	1			84

LMN—Lower motor neuron type of bladder
UMN—Upper motor neuron type of bladder
Mixed—Mixed motor neuron type of bladder
Sp—Indicates spontaneous return of bladder
Bl—Indicates bladder returned via one of the various nerve blocking procedures
TUR—Indicates bladder returned after a transurethral resection
Complete—Type of neurological lesion
Th—Thoracic

DISCUSSION

Without tidal drainage 84 out of 95 patients were catheter-free at one time or another prior to discharge Of the 11 patients who had never been catheter-free this writer does not believe that tidal drainage would have helped considering the findings 8 patients had cervical lesions 1 had bilateral upper extremity amputations 2 had had subarachnoid alcohol injections 1 had a permanent suprapubic cystostomy because of a penoscrotal fistula 1 had very unstable hyperreflexic autonomic responses refusing subarachnoid alcohol or rhizotomy and 3 preferred their catheters Three patients had thoracic lesions 2 were discharged before a completion of therapy (administrative reasons) and 1 suffered from severe trochanteric decubiti with suspicious amyloidosis

Of particular interest is the fact that 75 per cent of the catheter-free states occurred spontaneously Although the majority of the patients had bladder training to some degree it is hard to assess how much credit can be attributed to it corroborating previous studies[1-5] In addition 14 per cent became catheter-free following various blocks Therefore 89 per cent became catheter-free via conservative measures The majority became catheter-free within one year from the time of injury This would indicate that perhaps some of the patients in the group benefited by transurethral resection might have become catheter-free under conservative measures had we waited for at least a year

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FURTHER OBSERVATIONS ON TIDAL DRAINAGE

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In a previous study it was "concluded that tidal drainage and/or bladder training is not a panacea "[1] [2] That study was performed while patients were or had been on tidal drainage on the Spinal Cord Injury Service, V A Hospital, Long Beach, California

In an attempt to substantiate the original findings, a study was started wherein tidal drainage was discontinued as part of the formal management of our traumatic neurogenic bladders However, bladder training was continued because of its psychological effects, its reflex conditioning effects, and its possible prevention of bladder contracture [1] [2]

Each patient was interviewed upon discharge from the hospital about his bladder status The following information was ascertained 1) status of bladder (catheter-free or not), 2) method of becoming catheter-free, 3) vertebral level, 4) type of bladder (upper, lower, or mixed neuron), 5) time required to become catheter-free

RESULTS

Ninety-five patients were interviewed upon discharge Seventy-four were catheter-free whereas 21 still had catheters Of the 21 patients discharged with catheters, 10 had been catheter-free, requiring reinsertion of catheters due to complications, whereas 11 had never been catheter-free

Eighty-four patients were or had been catheter-free prior to discharge Sixty-three (75 per cent) became catheter-free spontaneously, 12 (14 per cent) by various blocks, 9 (11 per cent) by transurethral resection See table 1

Of the 84 patients, 36 had cervical lesions, 5 had thoracic 1–4, 11 had thoracic 5–8, 20 had thoracic 9–12, 12 had lumbar

Of the 84 patients, 75 had lesions of upper motor neuron type (39 complete and 36 incomplete), 8 had lesions of lower motor neuron type (3 complete and 1 incomplete), 1 lesion was of a mixed type

The period of time to become catheter-free among the 84 patients ranged from three weeks to 12 months for the group which did so spontaneously, except one who became catheter-free after 26 months, 4 to 24 months for the group with various blocks, 7 to 30 months for the group with transurethral resections

The vertebral levels of those patients who required reinsertion of catheters due to complications were distributed as follows 5 cervical 3 thoracic 7-12 and 2 lumbar

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Paper delivered before the Sixth Annual Paraplegia Conference, V A Hospital, Richmond, Virginia, October 23, 1957

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A PRACTICAL AID FOR QUADRIPLEGICS TO EMPTY LEG URINALS

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In an attempt to empty his leg urinal the tetraplegic usually spills the contents onto the latrine floors and/or wets his clothing and shoes. An attempt to empty the contents into the toilet bowl usually results in contamination of the distal tubing of the bag. Consequently the quadriplegic is dependent on outside assistance from an attendant.

In order to save attendants' time and make the quadriplegic more independent, especially at home, the following simple apparatus was devised. Figure 1, *A*, shows an ordinary shut-off lever clamp used on rubber tubing. In order to give the lever length, a two inch long copper tubing (¼ inch in diameter), flattened at one end, is riveted to the lever. A sheet metal strip (⅜ inch by 2½ inches) is soldered to the undersurface of the clamp. The modified clamp (fig. 1, *B*) is attached to the distal end of the urinal bag tubing. When the bag is to be emptied, the patient inserts the modified clamp into the slots of the toilet attachment (fig. 1, *C*). The toilet attachment consists of a rectangle of heavy wire (4½ inches by 8 inches) to one end of which is welded a rectangular piece of sheet metal (3 inches by 5 inches). The lower halves of the two sheet metal strips (⅜ inch by 2½ inches) are soldered vertically to the metal plate with the free ends adjusted to admit the metal horizontal strip of the modified shut-off clamp.

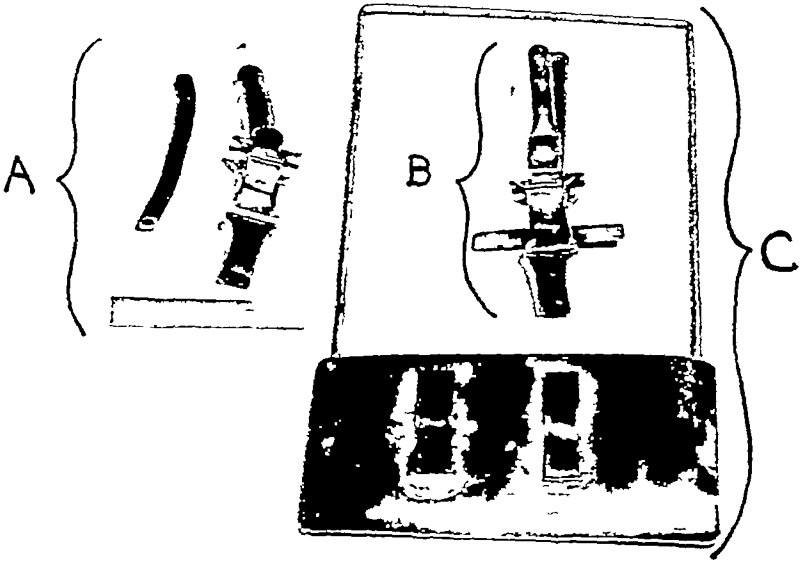

FIG. 1. *A*, *B*, modified shut-off lever clamp. *C*, toilet bowl attachment.

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SUMMARY

Out of 95 patients who had been managed without tidal drainage, 84 became catheter-free, of the 84 patients, 63 (75 per cent) did so spontaneously, 12 (14 per cent) with the aid of various blocks, and 9 (11 per cent) by transurethral resection

Based on previous studies as well as this study, the author cannot see the necessity for the use of tidal drainage [1-4]

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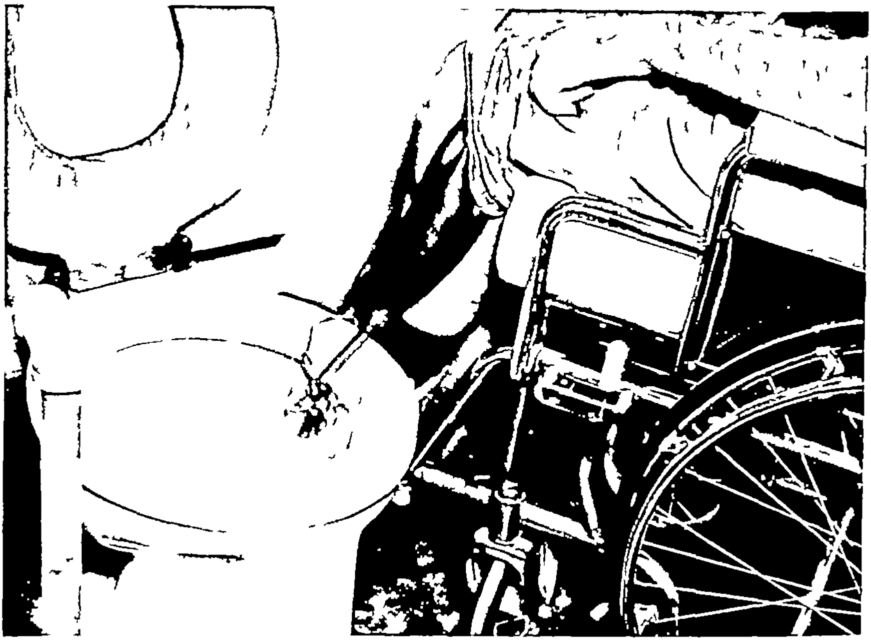

FIG 2 Device in action Note extended lever handle which quadriplegic is able to manipulate

The toilet attachment is bent to fit the toilet bowl rim Figure 2 shows the clamp of the urinal placed by the quadriplegic into the slots of the toilet attachment The lengthened lever handle can be managed by the quadriplegic's thumb or edge of the hand

SUMMARY

A modified shut-off lever clamp and toilet attachment are described in pursuing the objective of making the quadriplegic more independent

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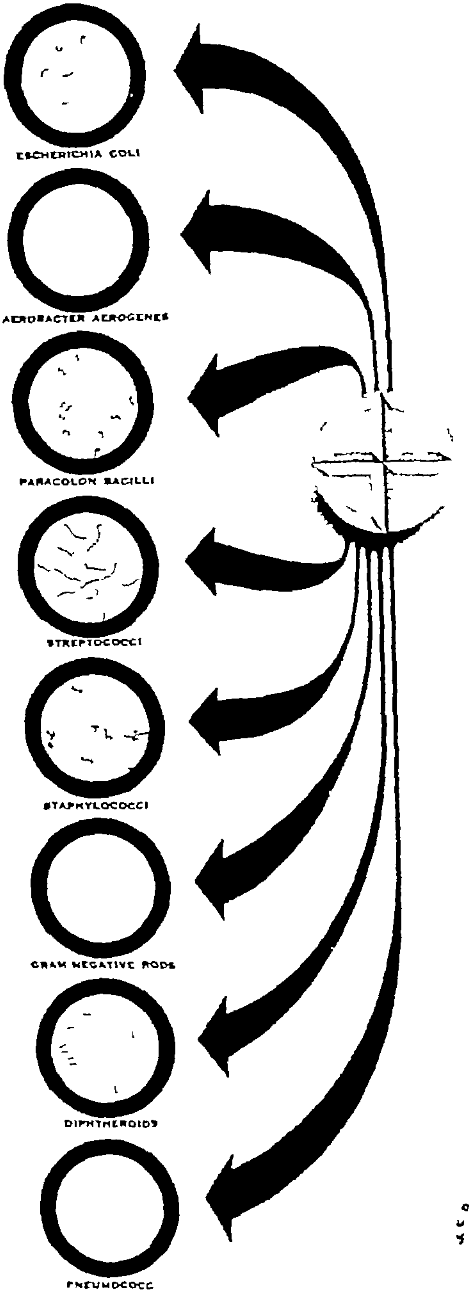

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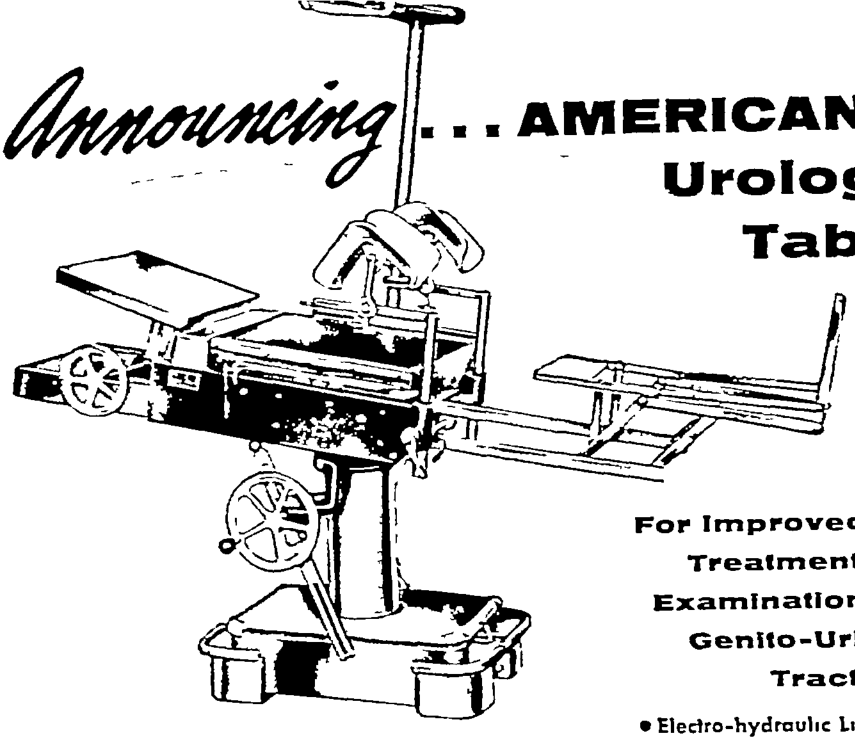

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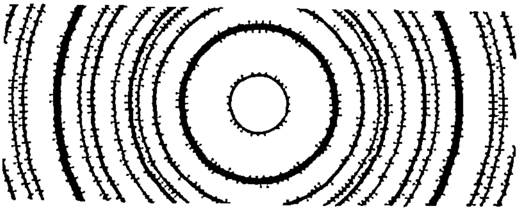

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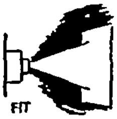

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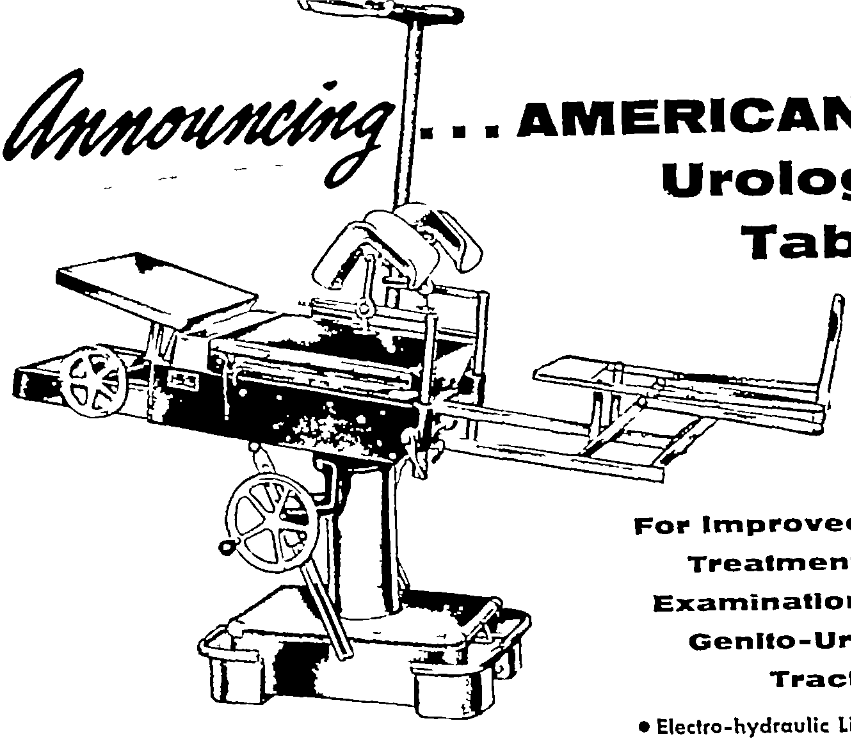

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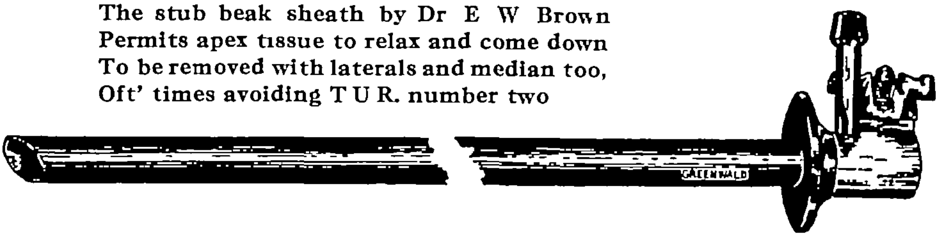

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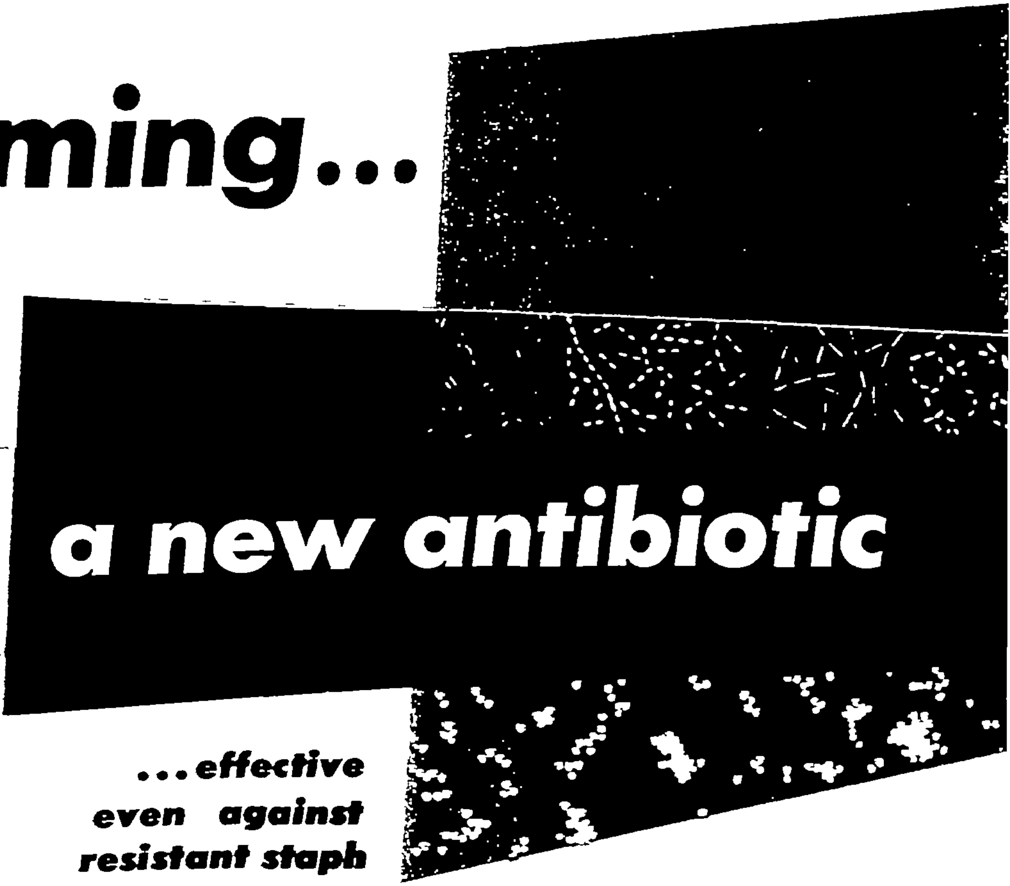

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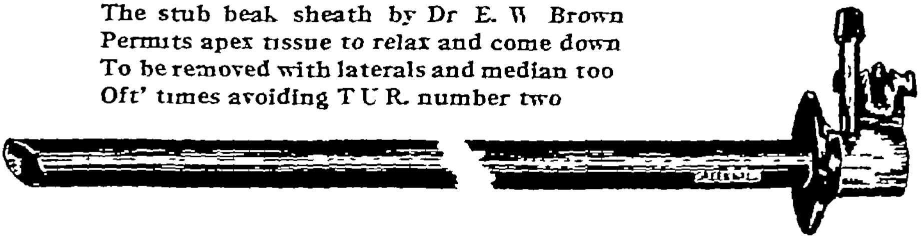

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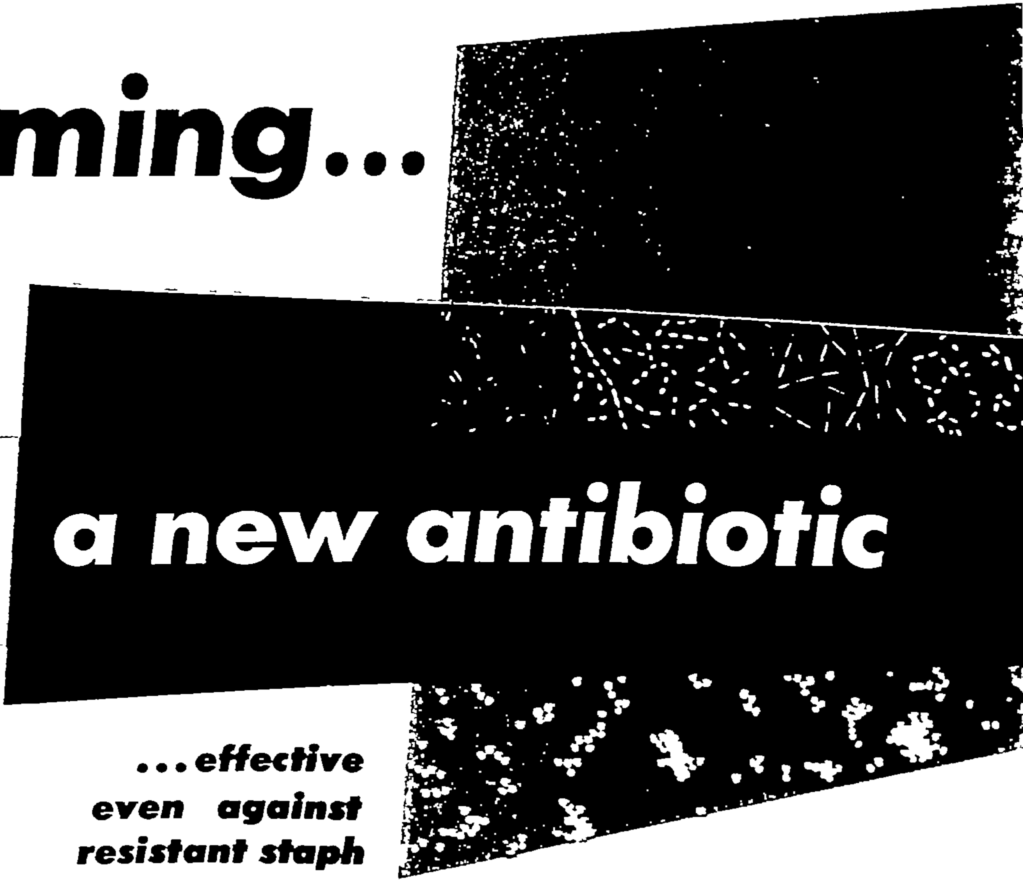

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There is a need for knowledge of actual basic anatomy and physiology of the sex relation, with the bearing of the varieties and frequencies of sexual intercourse on general health and pelvic disorder

Dr Dickinson has conducted a thorough re-examination of existing authorities, detailed measurements of a great number of cases are his authority for statements not only of the average but of deviations from the average

Some of the conditions described and illustrated conditions favorable or unfavorable for conception, conditions favoring or handicapping ideal sex intercourse, physical conditions productive of painful intercourse, anatomical findings in autosexuality

Actual facts replace the vagueness, the misconceptions, which have been all too prevalent, even recently

Treatment of all patients is surer, swifter, when backed up by certain knowledge

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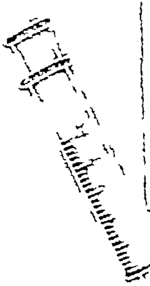
Check bladder and urethra
this **SIMPLE, WELL TOLERATED, ACCURATE** way

"Retrograde cystograms and urethrograms employing a 10 to 20 per cent solution of Skiodan furnish accurate information"*



TRAUMATIC RUPTURE OF URINARY BLADDER

Specimen shows bladder prostate urethra and ureters. Laceration at dome of bladder has produced hemorrhage and edema. Large hematoma adherent to musculature

*Robertson, J. P., and Headstream, J. W.: South. Med. Jour., 44:895 Oct., 1951

Solution 40 per cent
bottles of 50 and 100 cc.
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bottles of 50 cc.
Tablets of 1 Gm.
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acute and chronic prostatitis
nd following prostatectomy

FURADANTIN®

and of nitrofurantoin

ures or improves 4 out of 5 patients

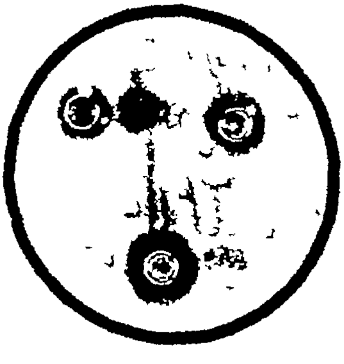
32% of 236 cases of acute and chronic prostatitis cured or improved with FURADANTIN[2]

	No patients	*Cured*	*Improved*	*Unimproved*
Acute Prostatitis	29	17	11	1
Chronic Prostatitis	207	49	117	41
Total	236	66	128	42

84% (142) of 170 cases of postprostatectomy infection responded favorably to FURADANTIN therapy[2] FURADANTIN "has been found to be highly effective in the treatment of chronic urinary tract infection following prostatectomy"[3]

In prostatitis and following prostatectomy, FURADANTIN offers these advantages ▪ rapid bactericidal action against a wide range of gram-positive and gram-negative bacteria and organisms resistant to other agents including Proteus and certain strains of Pseudomonas ▪ negligible development of bacterial resistance in 6 years of extensive use ▪ excellent tolerance—nontoxic to kidneys, liver and blood-forming organs No cases of monilial superinfection, crystalluria or staphylococcic enteritis ever reported ▪ safe for long-term administration

Evidence of the antibacterial action of prostatic secretion from a patient receiving FURADANTIN



Agar plate seeded with E coli Prostatic secretion of FURADANTIN treated patient was dropped into steel cylinders to prevent spreading of liquid. After incubation, zones of bacterial inhibition are clearly visible.

AVERAGE FURADANTIN DOSAGE IN PROSTATITIS
Acute cases 100 mg q.i.d until cured
Chronic cases 100 mg q.i d. for 10 to 14 days, depending on response, dosage may then be reduced to 100 or 200 mg daily for 1 to 3 months

SUPPLIED Tablets, 50 and 100 mg , bottles of 25 and 100
Oral Suspension, 25 mg per 5 cc. tsp , bottle of 60 cc.

REFERENCES 1. Barnes R. W., in discussion of Chinn J., and Bischoff, A. J Tr West. Sect. Am. Urol. Ass. 22 189 1955 2. Published reports and personal communications to the Medical Department, Eaton Laboratories. 3 Draper J W., et al. J Urol., Balt. 72 1211, 1954.

Additional references on FURADANTIN in prostatitis Trafton H. M., et al. New England J Med. 252 383 1955 Nordleet, C. M., Jr., et al. Tr Southeast. Sect. Am. Urol. Ass., Boca Raton, Fla., 1952, p 26 Schatten, W E., and Persky L. Am. J Surg. 86 720 1953. Abrams, M., and Prophete, B. Missouri M. 51:280 1954.

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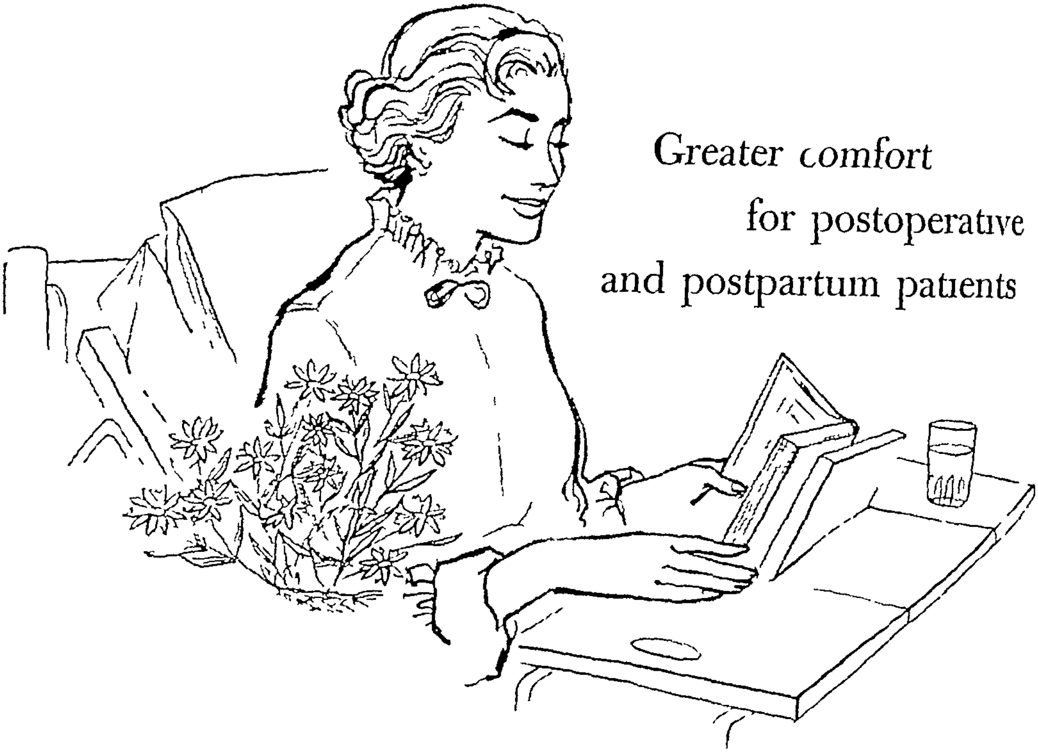

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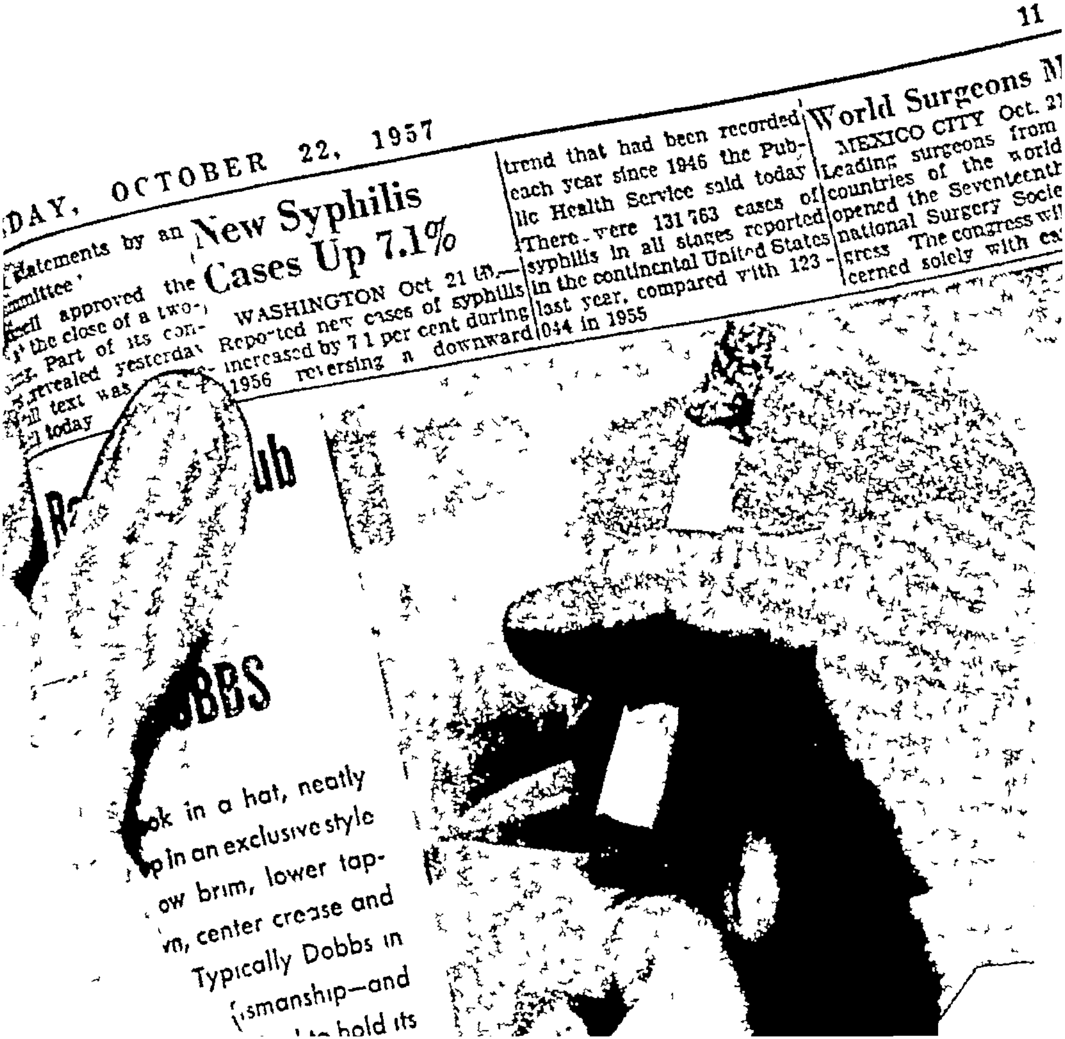

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DAY, OCTOBER 22, 1957

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New Syphilis Cases Up 7.1%

WASHINGTON Oct 21 (UP)—Reported new cases of syphilis increased by 7.1 per cent during 1956 reversing a downward trend that had been recorded each year since 1946 the Public Health Service said today

There were 131,763 cases of syphilis in all stages reported in the continental United States last year, compared with 123,044 in 1955

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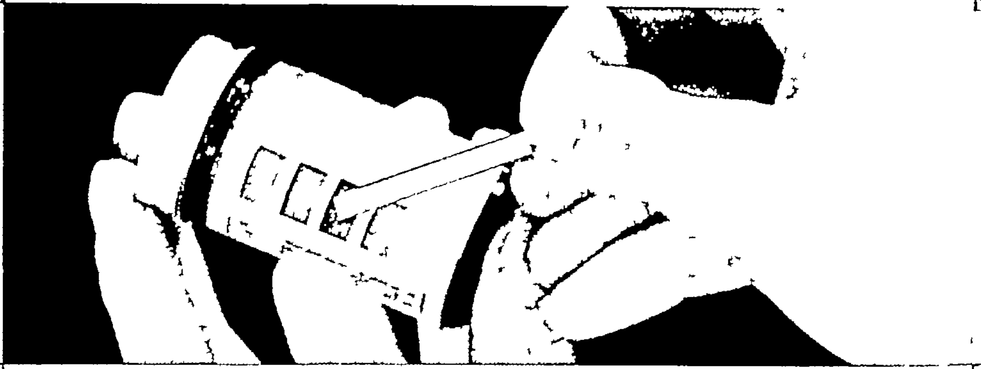

What is the meaning of "kidney threshold"?

The "kidney threshold" for any substance is the maximum amount of it that the kidneys will tolerate *in the blood* the excess will appear in the urine "Desirable" blood components, such as glucose and plasma proteins (albumin, globulin, fibrinogen), have a high threshold and normally remain in the blood "Undesirable" blood components, such as ketone bodies (acetone, acetoacetic acid, β-hydroxybutyric acid) and the metabolic wastes (urea, creatinine, uric acid), are low-threshold substances and are rapidly excreted into the urine

Source—Best, C H, and Taylor, N B The Physiological Basis of Medical Practice ed 6, Baltimore, The Williams & Wilkins Company, 1955, pp 448-450

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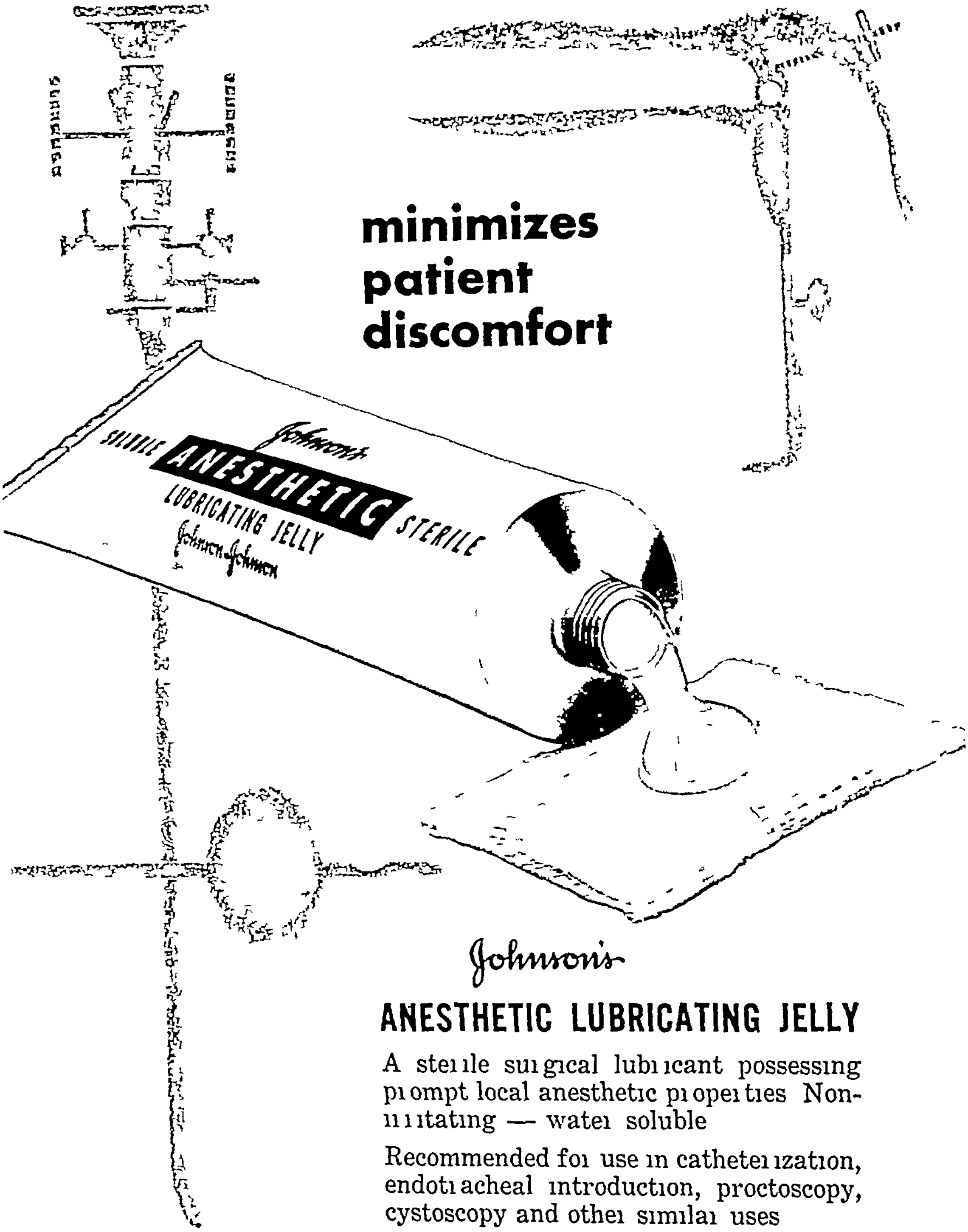

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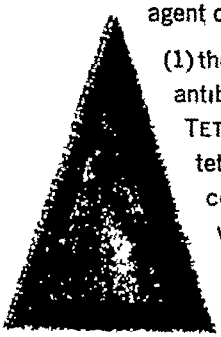

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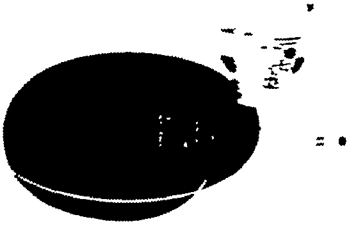

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TETREX (tetracycline phosphate complex)	125 mg
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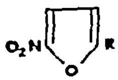

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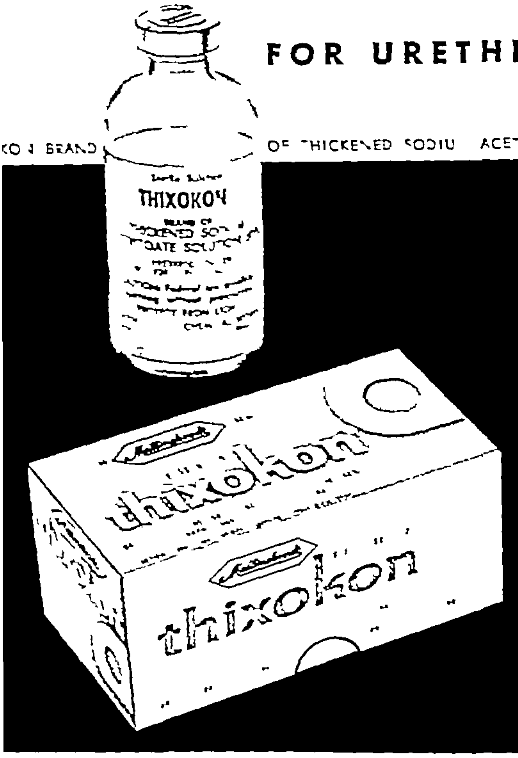

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1 Kaufman, J J Experiences with THIXOKON—A New Radiopaque Urethrographic Medium J Urol (Accepted for publication)

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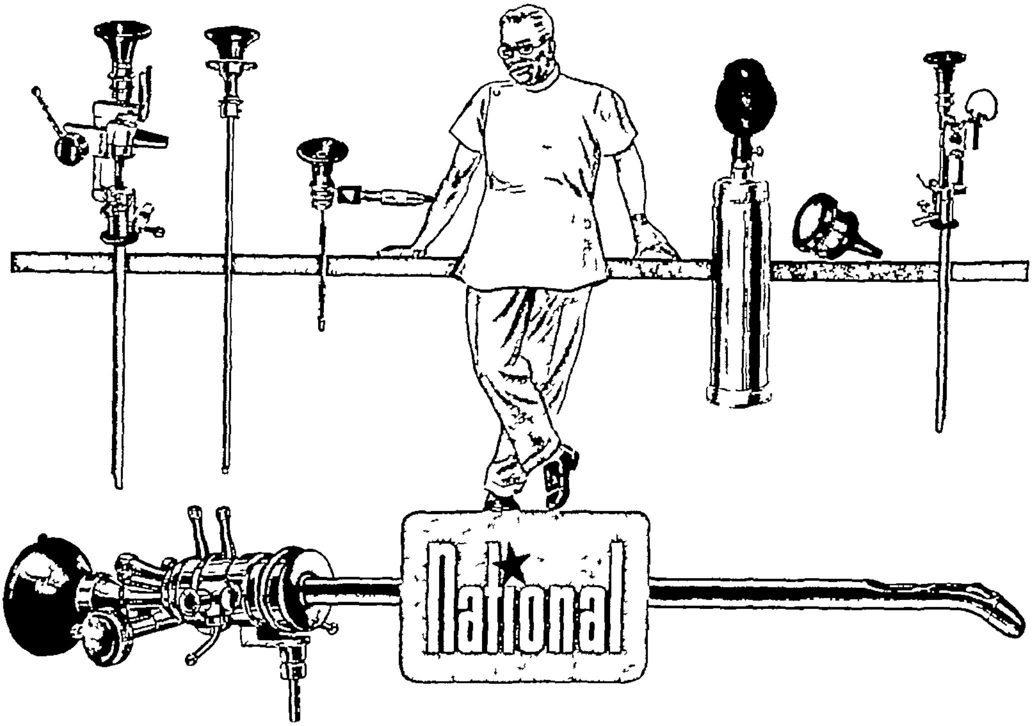

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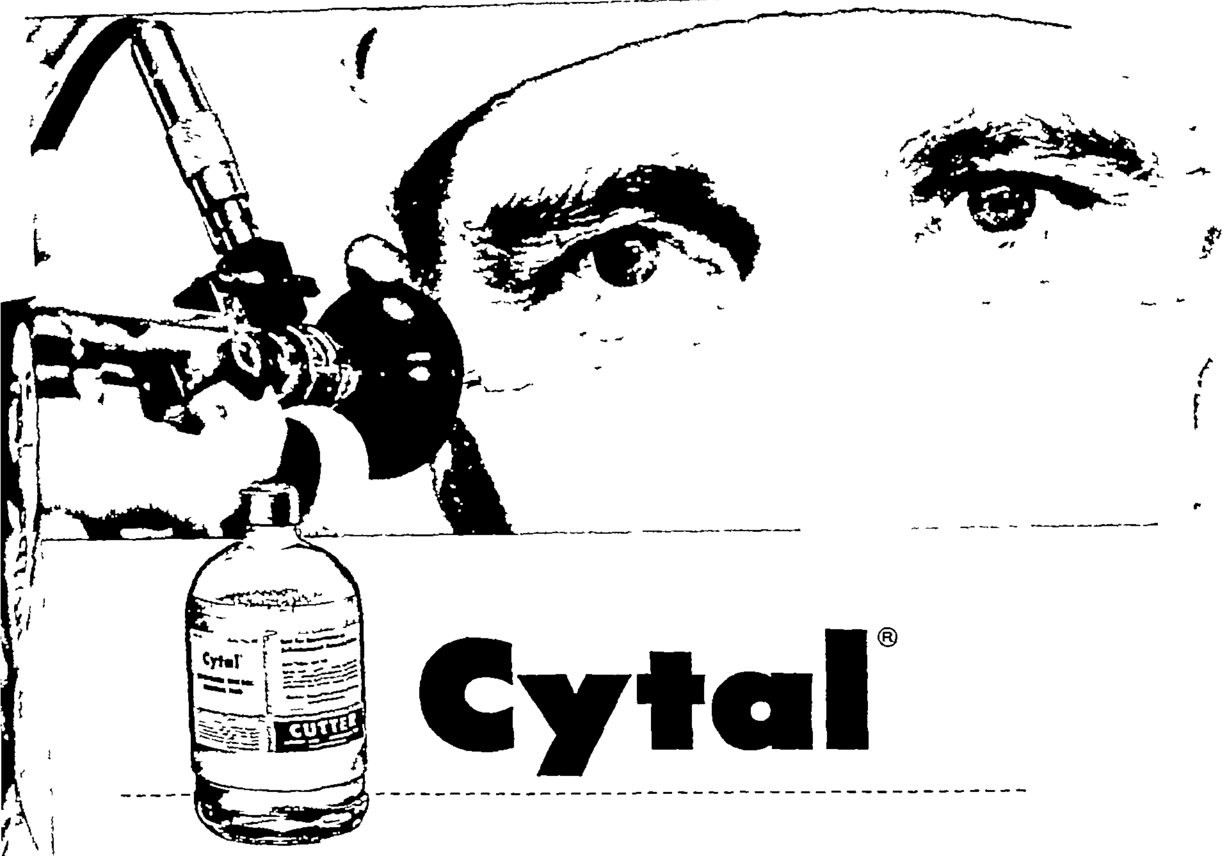

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In urinary-tract infections

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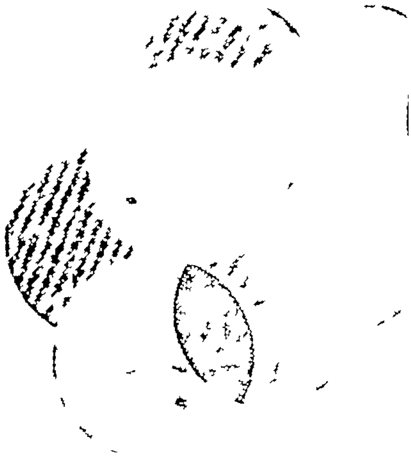

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LATTIMER, J K. and SPIRITO A L.: Clorpactin for tuberculous cystitis *J Urol* 73:1015 1018 1955

O CONOR VINCENT J: Clorpactin WCS-90 in the treatment of interstitial cystitis *Quarterly Bulletin, Northwestern Univ Med School* Chicago 1955 Vol. 29 No 4 Page 392 Winter Quarter

FLOCKS R. H and KADESKY M. C.: Medical Management of Urinary Tract Infections, *The Medical Clinics of N A* Sept 1956 (Saunders)

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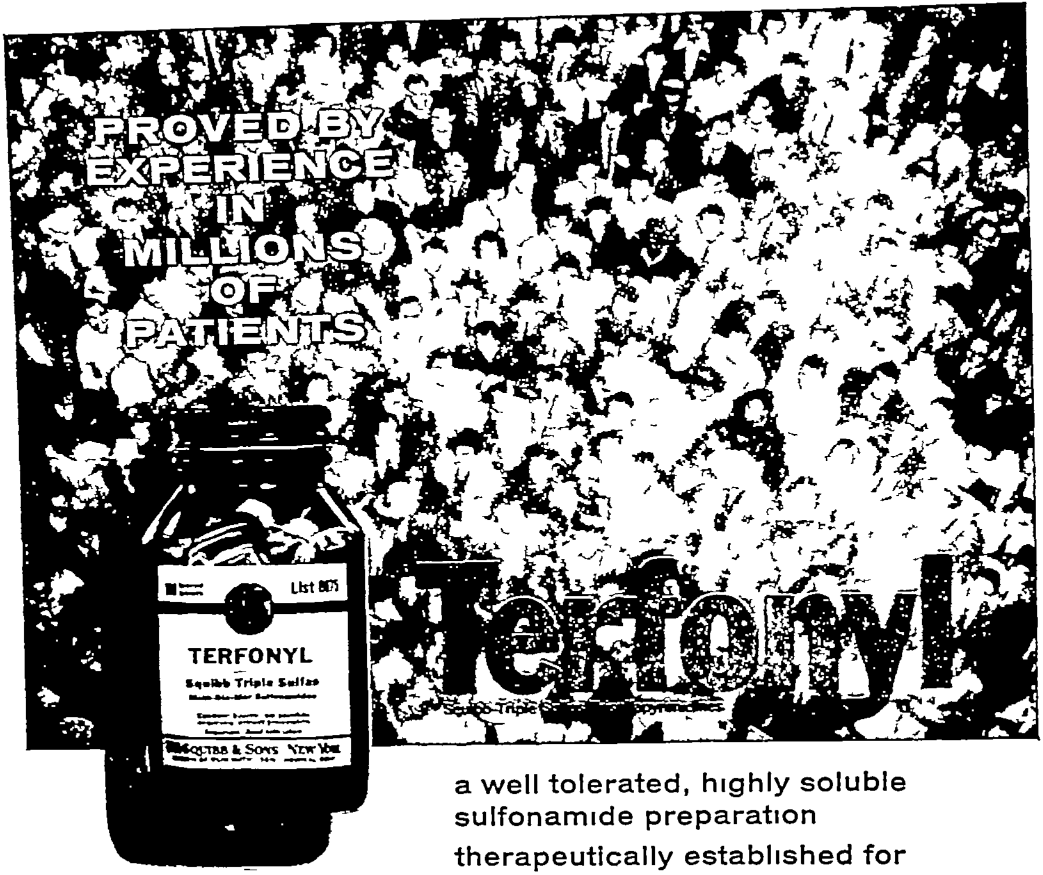

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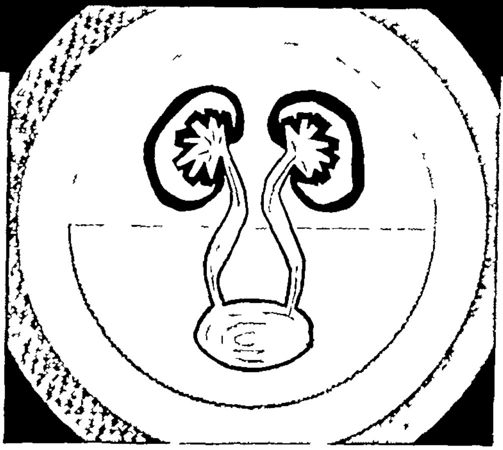

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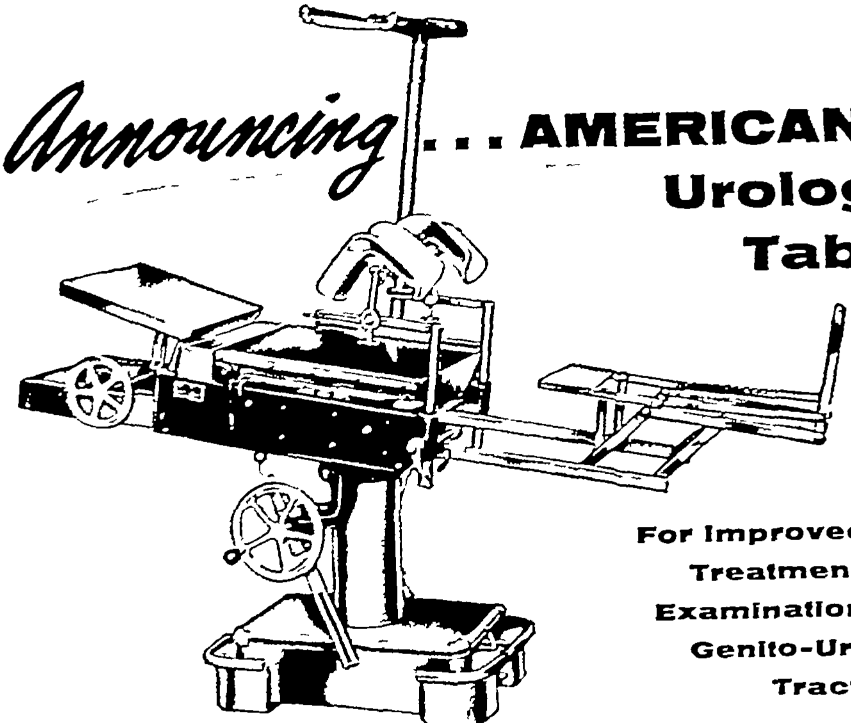

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*Lowsley O S and Kirwin T J Clinical Urology Baltimore The Williams & Wilkins Company 1956 p 618

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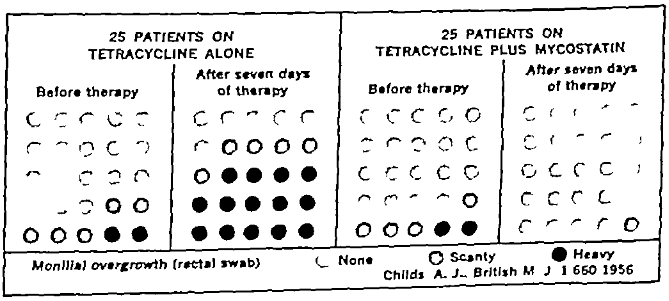

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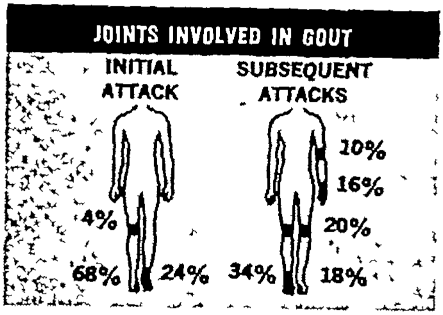

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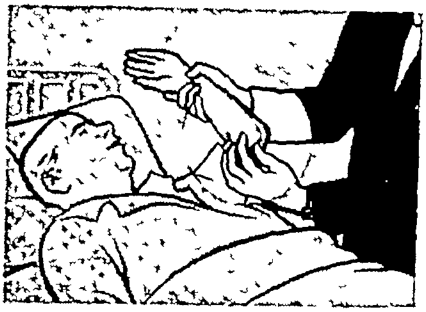

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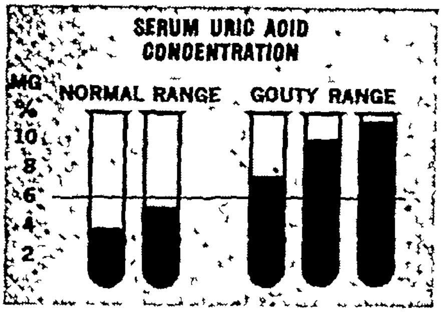

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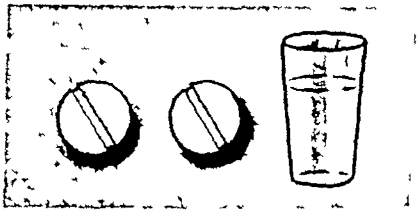

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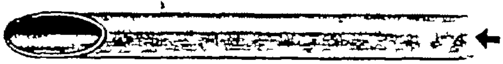
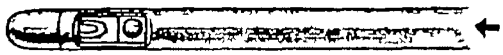
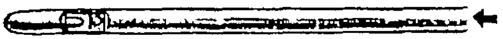


Open end pan endoscope sheath, Cat No 5451



Right angle telescope, Cat No 5452, used with 24, 26 and 28 Fr open end pan endoscope sheaths



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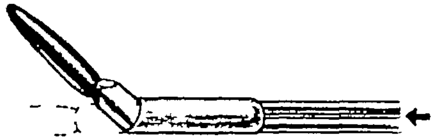

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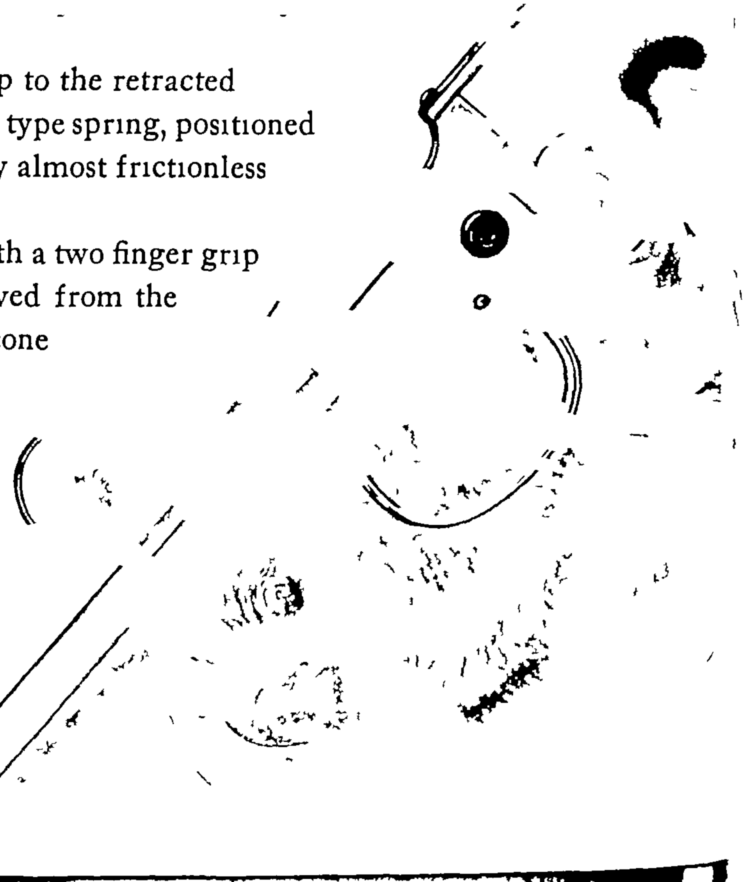

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A CLINCAL COMPARISON BETWEEN BENIGN SOLITARY CYSTS AND MALIGNANT LESIONS OF THE RENAL PARENCHYMA

CHARLES H DET SHIVERS* AND HERBERT D AXILROD

From the Department of Urology, Atlantic City Hospital, Atlantic City, N J

Many urologists have emphasized the difficulties encountered in attempting to differentiate benign solitary cysts from adult parenchymal renal tumors on a clinical basis While this is undoubtedly so when examined from a single point of view, such as radiological study alone, an interpretation based on all the available clinical information, as suggested by Prather, frequently categorizes the lesion On the basis of this fact, we believe it would be interesting to again draw a clinical comparison between benign solitary cysts and malignant lesions of the renal parenchyma

In the past, renal cysts have been considered a rather uncommon lesion but since our paper was published on this subject in 1953, we have encountered a larger number of cysts than tumors, and more numerous reports have appeared in the literature This increase in the incidence of benign solitary renal cysts, in recent years, is probably a relative one rather than a true picture, as the cases presenting obscure abdominal symptoms today are more carefully surveyed than they were in the past Cysts are apparently more frequent in females than renal carcinoma, while renal neoplasms are much more common than cysts in men Extraurinary tract symptoms, such as vague gastrointestinal discomfort from pressure of the mass on adjacent abdominal organs or respiratory symptoms or shoulder pain from pressure on the diaphragm, have been much more common with cysts than with neoplasms Also contralateral symptoms may be more frequent with cysts

Hematuria is the outstanding early symptom in 60 per cent of renal neoplasms The bleeding is intermittent but seldom profuse With benign solitary renal cysts, gross and microscopic hematuria are rare Renal pain ranks second as an early symptom of tumor It is the presenting symptom in approximately 22 per cent of cases but it is uncommon in cysts The renal pain is probably due to an expanding lesion confined by the renal capsule, with an increase in pressure within the capsule Although the usual benign cyst grows outward and away from the kidney, causing pressure on adjacent organs, an occasional one may be located deep within the renal parenchyma and in such instances renal pain may be present This may also occur if the urinary drainage is impeded by the pressure of a large lower pole cyst on the upper ureter The physical characteristics of a palpable mass do not seem to be of much help in the differential diagnosis A low grade fever, due to necrosis within the tumor, is said to be present in about 20 per cent of cases of renal carcinoma, but this may also occur in infected renal cysts Anemia and weight loss weigh in favor of tumor while the

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Read at the meeting of the New England Section of the American Urological Association in Providence Rhode Island April 25 1957

* President, American Urological Association 1956-57 *Editor*

demonstration of metastases positively establishes the diagnosis The study of the urinary sediment for blood, pus and with Papanicolaou stain for tumor elements may yield important clues As with all work of this type, a positive report is of much more value than a negative one and the identification of tumor elements is much more likely to be positive in renal pelvic tumors than in parenchymal lesions Direct translumbar aspiration of a renal cyst or renal cystograms, as recommended by Vest and Ainsworth, may establish a diagnosis, but we are not in favor of this procedure because of the hazards which may be encountered in using this method

When considering x-ray studies, excretory urograms are frequently of more help than retrograde studies because of better visualization of the parenchyma In most cases of cyst, even though the calyces may be extensively deformed, the normal terminal configuration of the minor calyces may often be retained in contradistinction to renal tumors in which it may be completely lost If the benign cyst grows away from, rather than into the parenchyma, the true pelvis is rarely impinged upon In neoplasms, the renal outline is often enlarged, in cysts, it is frequently normal and can be differentiated from the cyst outline The cyst is smooth and is less dense than the kidney The psoas line can frequently be seen through the cyst, whereas in solid tumors it may be obliterated Calcification is seldom seen in the wall of a solitary cyst, whereas approximately 15 per cent of renal tumors show the presence of calcium The obliteration of a calyx favors cancer while the distention of a deformed calyx is in favor of cyst Adhesions which result in poor diffusion in perirenal air insufflation favor tumors We have had no experience with aortograms or nephrotomograms

Clark, Goade, Rudy and Rockwood have pointed out that certain complications must be kept in mind when dealing with solitary renal cysts, such as the impairment of renal function by pressure atrophy of the adjacent parenchyma, the possibility of carcinoma in the wall of the benign cyst, the danger of trauma which could result in rupture and precipitate an acute abdominal emergency and the possibility of unexplained hypertension produced by the compression of the renal vascular supply by such a mass

We have selected five cases with which we hope to contrast the findings in cyst and tumor

Case 1 is a 58-year-old man with a history of a chronic nonspecific prostatitis of two years' duration, but no other genitourinary complaints On one occasion he noted gross hematuria with the blood well mixed with the urine and containing many small clots On physical examination, carried out the same day, neither kidney was palpable and there was no costovertebral angle tenderness An abdominal mass was not palpable His temperature was normal The urine was loaded with red blood cells and on cystoscopy, a worm-like clot was seen protruding from the right ureteral orifice

Case 2 is a 64-year-old white man, with a history of left upper quadrant pain of five years' duration He had never had hematuria or any other urinary symptom On examination, neither kidney was palpable but there was mild left costovertebral angle tenderness on fist percussion Urinalysis was negative, with no

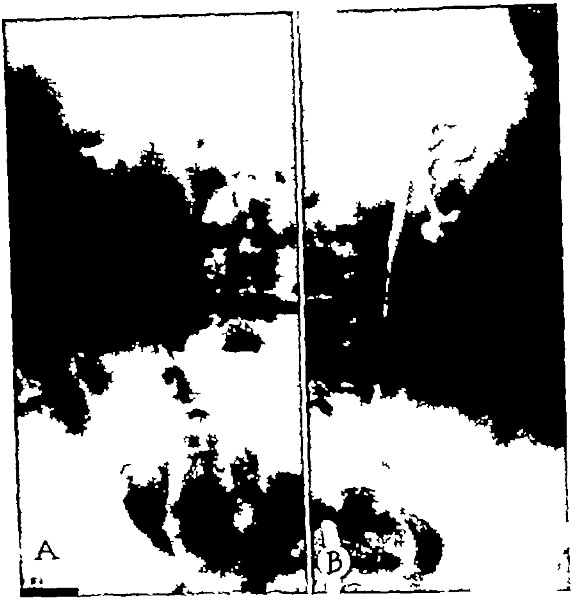

FIG 1 A, case 1 Malignant tumor, upper pole of right kidney B, case 2 Multiloculated retention cyst, lower pole of left kidney

microscopic red blood cells There was no anemia and the temperature was normal

Examination of the retrograde pyelogram in case 1 (fig 1, *A*) reveals broadening of the upper pole of the right kidney There is compression of the upper major calyx with incomplete filling and no evidence of impingement on the true pelvis A filling defect, due to a blood clot, is seen in the pelvic ureter The retrograde pyelogram in case 2 (fig 1, *B*) shows a spreading of the middle and lower major calyces with dilatation of the deformed calyces but no obliteration There is no involvement of the true pelvis Operation revealed an advanced renal cell carcinoma in case 1, while in the second case, the lower pole of the left kidney was largely replaced with a multiloculated retention cyst

Case 3 is a 65-year-old white man who had no urinary symptoms but was admitted to the Atlantic City Hospital for study to determine the cause for lassitude and a persistent unexplained hypochromic anemia with a hemoglobin determination of about 8 0 gm per 100 cc There was also a persistent evening temperature rise to 101F Urinalysis was completely negative with no microscopic hematuria Careful physical examination was unrewarding but an intravenous urogram suggested a space-occupying mass in the upper pole of the right kidney This was confirmed by retrograde pyelography

Case 4 is a 66-year-old Negro, who was admitted to the Atlantic City Hospital with no upper urinary tract complaints During a preoperative workup, prior to suprapubic prostatectomy, excretory urography revealed a mass in the lower pole of the left kidney Except for his benign prostatic enlargement, physical examination, including a blood count and repeated urinalyses, was completely

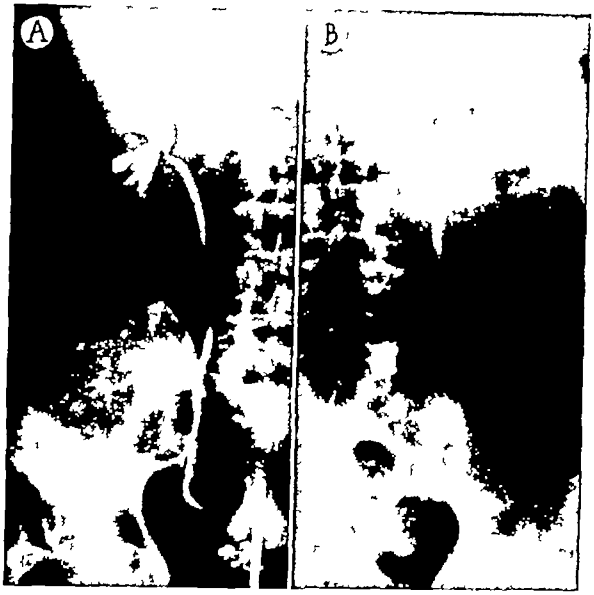

Fig 2 *A*, case 3 Malignant tumor, upper pole of right kidney *B*, case 4 Solitary cyst, lower pole of left kidney

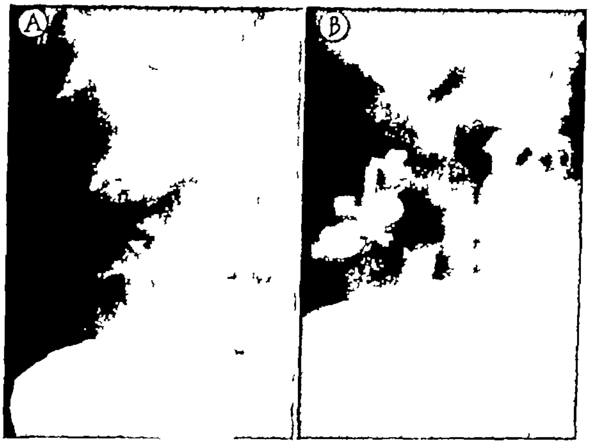

Fig 3 Case 5 *A*, intended cholangiogram demonstrates lower pole cyst, right kidney *B*, retrograde pyelogram of same kidney

negative His temperature was normal Two subsequent excretory urograms did not show any change in the mass

Examination of the retrograde pyelogram in case 3 (fig 2, *A*) reveals an enlargement of the upper pole of the right kidney There is elongation of the upper major calyx with partial obliteration and impingement on the true pelvis There is some flattening of the middle calyx The excretory urogram in case 4 (fig 2, *B*) shows elongation and deformity of the lower calyx due to a space-occupying mass The deformed calyces are not distended and there is distortion of the pattern of the terminal ends of the calyces The true pelvis is not involved Surgery in case 3 revealed a large clear cell adenocarcinoma of the upper pole of the right kidney In case 4, the lower pole contained a deep-seated benign solitary cyst measuring 5 cm in diameter In our opinion, the pyelographic deformity in case 4 was more suggestive of a renal tumor This may be explained by the fact that the cyst, in this case, was situated deep within the renal parenchyma

The last case is a 58 year-old-white woman admitted to the Atlantic City Hospital with nausea and intermittent right upper quadrant abdominal pain of seven years' duration When her symptoms first developed a cholecystectomy for cholelithiasis was done, but the symptoms continued with increasing severity There had been no urinary symptoms or elevated temperature Physical examination and all laboratory work, including blood count and urinalyses were negative Forty cubic centimeters of cholografin were given intravenously for the purpose of visualizing the bile ducts, but instead obtained for us a very satisfactory excretory urogram (fig 3 *A*) This reveals some elongation and distortion of the lower major calyx and an outline of what appears to be a cyst wall springing from the lower pole of the kidney The right retrograde study (fig 3, *B*) shows considerable dilatation and flattening of the calyces with malrotation of the kidney At operation, a large benign solitary cyst was removed from the anterior surface of the lower pole of the kidney

SUMMARY

Until a reliable blood or biological test for the detection of urinary tract malignancy is devised, the ultimate differentiation of renal tumor from benign cyst will probably always depend on surgical exploration However, careful consideration of all the aspects of the clinical picture together with detailed consideration of pyelographic changes will lead to a correct preoperative diagnosis in a surprisingly large percentage of cases

121 S Illinois Ave Atlantic City, N J

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MALIGNANT PHEOCHROMOCYTOMA WITH VOLUNTARY ABILITY TO ELEVATE BLOOD PRESSURE

CHARLES L RANSOM, RALPH R LANDES AND C G GADDY

From the Memorial Hospital, Danville, Va

The increasing number of pheochromocytomas reported indicates that the physician, aided by diagnostic advances in catechol determinations, retroperitoneal pneumography, adrenolytic and provocative drugs, is becoming more aware of these tumors as a clinical entity and a curable form of hypertension We wish to present a case of malignant pheochromocytoma with some rather unusual clinical aspects and review some of the current concepts regarding these neoplasms

CASE REPORT

H A , 37-year old white man, had been followed by one of us (C G G) over a period of three years Physical examinations had disclosed no abnormalities His blood pressure on several routine office visits was 132/65 mm Hg On the day of admission to the hospital, because of a strange feeling in his chest and a sense of suffusion throughout his face when bending over or flexing himself laterally, he had come directly from work to his physician At this time, the blood pressure was 230/110 mm Hg, his pulse rate was 70, and a firm, nonballottable mass could be felt below the left costal margin When the blood pressure returned to normal, it could again be elevated at will by the patient with lateral flexion of his trunk, but no direct palpation could reproduce the phenomenon

It is of interest to note that three years earlier, an upper gastrointestinal tract x-ray had been taken for a gastric complaint and it is seen in retrospect that there was a filling defect in the left upper quadrant with lateral displacement of the stomach (fig 1, *A*)

The patient was admitted to the hospital where complete blood count and urinalysis were within normal limits Electrocardiograms were not indicative of chronic heart disease, and no evidence of retinal arterial changes could be detected Intravenous pyelograms demonstrated a mass lying superior to the left kidney with distortion of the renal calyceal and pelvic structures (fig 1, *B*) The intrarenal distortion was more marked than ordinarily produced by a benign extrinsic mass and the possibility of a malignant pheochromocytoma was entertained His resting blood pressure was 132/65 mm Hg, and when the patient attempted to elevate it through lateral flexion of the spine, there was a transitory rise to 220/110 mm Hg, which in a few minutes leveled back to 175/110 mm Hg No further gymnastics could raise the blood pressure A relative bradycardia was noted during elevations in blood pressure Regitine was administered intravenously at this time and the blood pressure fell to

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Read at annual meeting of Mid Atlantic Section of American Urological Association Virginia Beach, Va , March 21-24 1957

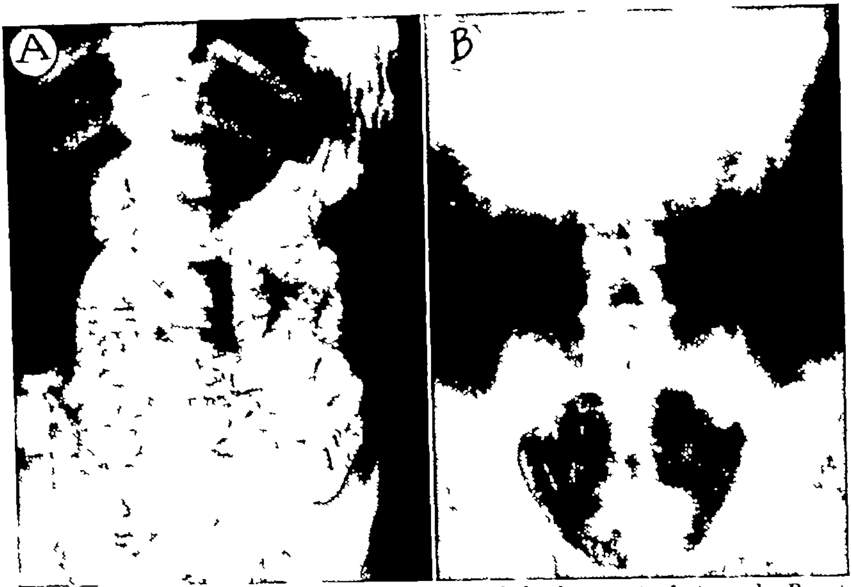

FIG 1 *A*, gastrointestinal film shows left lateral displacement of stomach *B*, intravenous pyelogram shows large mass superior to left kidney and renal calyceal and pelvic defects

135/62 mm Hg within two minutes, which was interpreted as a positive test Clinical evidence and laboratory data strongly indicated a pheochromocytoma of the left adrenal medulla with the pyelographic appearance suggestive of malignant renal invasion

A direct lumbo-dorsal approach was elected under pentothal curare anesthesia A 15 gauge intravenous needle was first introduced and an internist (C G G) stood by with a two-way apparatus to administer either regitine or levophed as the occasion indicated The twelfth rib was removed and a Nagamatsu osteoplastic flap was employed with the tenth and eleventh ribs being transected, thus moving the diaphragm superiorly The kidney was found to be involved in a large globular mass about the size of a football Despite our generous exposure, only about the lower third of the neoplasm could be exposed The renal pedicle and the entire medial portion of the tumor appeared to be inextricably involved with the aorta and stomach in one amorphous mass The tumor filled the entire left infradiaphragmatic space but was not adherent superiorly to the diaphragm Frozen section biopsy of the tumor capsule was reported as a neuroblastoma but was later shown on permanent section to be a malignant pheochromocytoma With aortic and intestinal fixation it was our opinion that the mass could not under any circumstances be removed, and the incision was closed Despite manipulation incident to evaluation of the tumor size, there was no marked fluctuation in blood pressure

Postoperatively the patient's course, supported by whole blood and levophed, was steadily downhill It appeared after the first hour in the recovery room that the patient's lack of response was attributable more to direct blood loss than

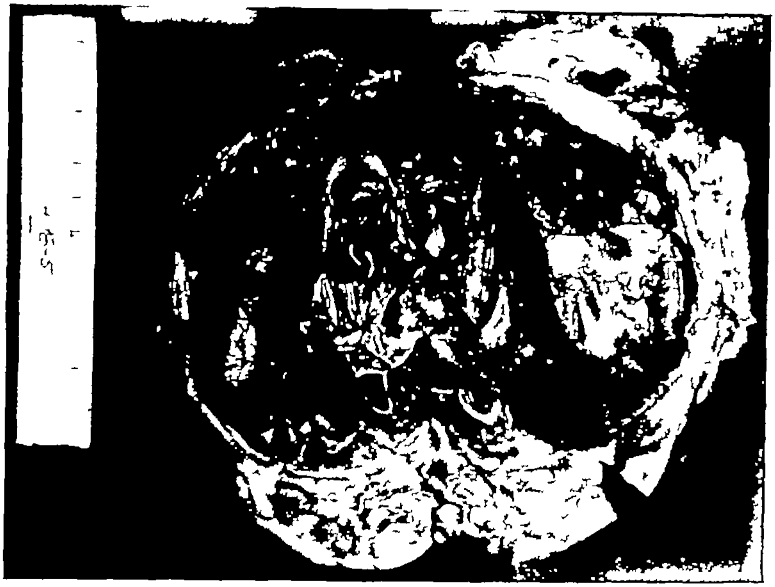

FIG 2 Tumor seen superior to kidney

to any phenomenon peculiar to a pheochromocytoma At the time of surgery, bleeding had been minimal but in freeing up the mass, a blood vessel could have been torn inadvertently Within several hours the patient's abdomen became distended and an 18 gauge needle, introduced into the peritoneal cavity, withdrew pure blood While in the recovery room, the patient's incision was reopened releasing large quantities of fresh blood The patient, despite 12 pints of blood, was still in shock and expired 14 hours postoperatively

At autopsy the mass was found to weigh 1300 gm and to completely fill the entire left infradiaphragmatic space, being adherent to the stomach and aorta with great distortion of the left kidney, and invasion of the renal parenchyma (fig 2) In the left adrenal artery leading from the aorta, a 1 mm triangular rent was discovered The pancreas was flattened to almost paper thinness The tumor, containing a large amount of necrotic, grumous material, collapsed like a balloon when opened There were no osseous, pulmonary or cerebral metastases

Microscopic examination Sections of the tumor mass show it to have a markedly thickened fibrous connective tissue capsule in which are seen diffusely scattered and focal aggregates of lymphocytes The tumor cells are markedly pleomorphic, stellate, fusiform and polyhedral showing nuclei which range from small to gigantic in size The nuclear chromatin is heavily and diffusely scattered Multinucleated cells are seen There are irregular fibrous connective tissue trabeculae surrounding islands of pheochromoblasts (fig 3) Diagnosis Malignant pheochromocytoma

Bio-assay of the tumor, performed by Dr Eugene A Conrad of the Bowman Gray School of Medicine, yielded 4122 mg /gm norepinephrine and 0078 mg /gm of epinephrine with a total catechol amine level of 420 mg /gm This

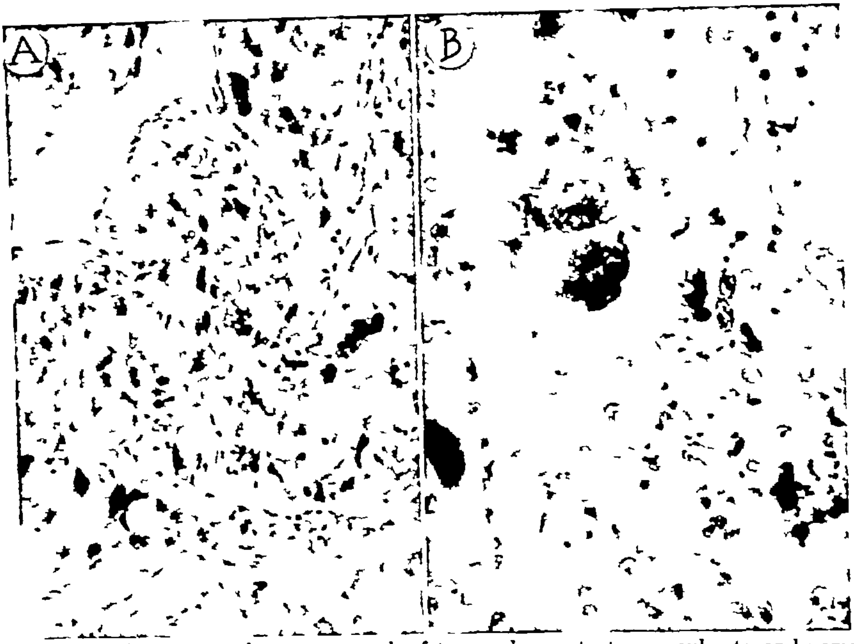

FIG 3 A low power photomicrograph of tumor demonstrates vascularity and various shaped pheochromoblasts B, high power photomicrograph demonstrates pheomorphism with nuclear chromatin

is barely above a normal level of 4 mg/gm The low figure is no doubt attributable to delay in analysis and accidental defrosting of the refrigerator for several days, with a resulting loss of activity Bio-assay method utilizing rat colon and uterus is also at the best 80 to 90 per cent accurate

The higher percentage of norepinephrine probably accounts for the bradycardia when the pressor effect was at its height While most pheochromocytomas containing high norepinephrine content produce a sustained hypertension (Goldenberg), this tumor produced paroxysmal hypertension The literature on pheochromocytomas contains numerous references to patients precipitating a pressor episode when lying on their side, but we believe it is unique that this man could stand upright and with lateral flexion voluntarily and consistently precipitate an attack which no amount of flank manipulation could duplicate

This tumor, which weighed 1300 gm, is the largest reported Pyle reported a malignant pheochromocytoma of 1070 gm Borch-Johnsen reported the largest benign pheochromocytoma which weighed 2000 gm

Our tumor, on the basis of adherence to the aorta and stomach, with renal invasion, can be included as a case of malignant pheochromocytoma

COMMENT

The incidence of malignancy in pheochromocytoma is from 8 to 11 per cent in the larger series Graham reported 24 of 207 collected cases, or 11 per cent as malignant, including 11 with gross invasion or metastases McKeith of England compiled 152 cases of pheochromocytoma of which 15 (10 per cent) were malignant. Six of these malignant tumors were bilateral. Cahill reported that 8 per cent of 139 cases were malignant. In the smaller series of cases, the rate of malignancy may seem higher. Cahill noted that two of his 14 cases were malignant and Sprague and associates and Kvale, four of 25. Geschickter in commenting on eight cases of pheochromocytoma in 1935 believed that malignant tumors were as frequent as benign growths. At Mayo Clinic 15,984 autopsies performed between 1928 and 1951 revealed only one malignant pheochromocytoma with metastases (Minno and associates).

The incidence of malignancy in paragangliomas is higher. Three of 17 cases of paraganglioma of the organ of Zuckerkandl have been reported as malignant, all three having metastases and two of them exhibiting pressor activity (Haug and Baker).

All bilateral pheochromocytomas were thought at first to be malignant. Eisenberg and Wallerstein compiled 53 cases of pheochromocytoma in 1932. Five of these were both malignant and bilateral. Calkins and Howard with Colston presented the cases of an aunt and her niece with bilateral tumors diagnosed as benign on the basis of both the surgery and histopathology. However, one of the patients later died with metastases. In their review of the literature, 17 bilateral cases were found, five of which were malignant, an incidence of about 30 per cent. More recently, Roth and associates cited the case of three siblings with bilateral tumors, all benign. There appears to be an increased incidence of malignancy in bilateral pheochromocytomas over that found in solitary tumors.

There is no apparent age or sex predominance within the adult range (Tamura and Lawrence). Pheochromocytomas are not common in children, about 35 having been reported (Smid and Dushane). Malignant tumors in children are rare. Evans and Steward believed that their case of a 14-year old colored girl should be considered malignant, on the basis of the microscopic findings. Espersen reported a malignant pheochromocytoma in a 10-year old boy. Although over 40 cases of pheochromocytoma in pregnancy have been presented in the literature, none has been malignant (Brann, Puryear and Landes).

The presence or lack of pressor activity in these malignant tumors has occasioned considerable discussion. The early papers dealt entirely with cases exhibiting no pressor activity and the impression was given that malignancy and a normotensive state were always co-existent (Edward, Eisenberg and Wallerstein, McGavack and associates). Later cases have refuted this generality. Chamovitz believes that the malignant pheochromocytomas with normal blood pressure pursue a more rapidly progressive course with widespread metastases than those exhibiting hypertension, either sustained or paroxysmal. Kvale's four cases of malignant pheochromocytoma found in a series of 25 were in the 11 patients with sustained hypertension. Cahill (1954) feels that when malignancy occurs, the hypertensive factor is seen early in the disease and then the pressor symptoms wane as the tumor grows and metastases occur. Death then takes place following the cachexia of malignancy without any pressor symptoms in the latter part of the disease. Schwarzhoff does not believe that the metastases exhibit hormonal activity, however, several authors have noted functioning metastatic tumors postoperatively following the removal of the original focus (Bannon and Allen, Kimberly, Richards and Hatch, Brines and Jennings)

One of the factors complicating any valid appraisal of malignant pheochromocytomas is the criteria to be established for diagnosis Even the so-called benign tumors may exhibit characteristics, such as pleomorphism and invasion of blood vessels, which in other tissue would be accepted as prima facie evidence of malignancy One hundred per cent of these tumors, according to Roth and associates, exhibit one or more of the features which among other species of new growths would be indicative of malignancy Some believe that cellular pleomorphism does not invariably indicate the presence of malignancy (Chamovitz and Fanger) Brines and Jennings would insist upon invasion in lieu of metastases as a criterion of malignancy and Spatt believes the only indication of malignancy is the presence of metastases All of these tumors, both benign and malignant, are very vascular and the cells lie in close relationship to the capillaries and blood sinuses, thus, any hormones formed by the tumor cells readily gain access to the bloodstream Even mature cells escape into the bloodstream with a fate unknown, probably destroyed in the lung capillaries The diagnosis of malignancy is on this account rendered more difficult (Blacklock and associates, Colston) Many of the malignant cells show the same characteristics as the simple tumors and several cases have been reported in which the pheochromocytomas were diagnosed as benign only to have the patient later die with generalized metastases (Chamovitz and Fanger, Colston, Soffer and associates, Thorn and associates)

It is interesting to speculate on the lack of hypertension in some of the malignant pheochromocytomas and attribute this quality to immature cells of the pheochromoblastic group However, most of these malignant tumors have some mature cells exhibiting a positive staining with dichromate salt (Chamovitz and Fanger) 'The pathologist is equally perplexed by the infrequency of metastasis in the face of cellular dedifferentiation and the paradoxical ability of these anaplastic cells to manufacture hormonal principles" (Roth and associates) While chromaffin and Gomori's azocarmine stains are suggestive of cells secreting a pressor substance, neither test is specific (Tamura and Lawrence)

Although evidence of pressor activity may or may not be present, the clinical manifestations of a malignant pheochromocytoma are often protean in nature Adrenal cortical deficiency may be simulated (McGavack and associates) or the onset of the disease may be heralded by signs and symptoms referable to the metastases Widespread dissemination of malignant cells into the lymph nodes, liver, brain and lung fields has been found with a seeming predilection for the cervical region Thus the patient may initially be seen with neurological findings of paralysis or hemiplegia (Cross and Pace, Kimbro, Remine and associates) A locally invasive malignant pheochromocytoma of the urinary bladder exhibiting pressor activity was diagnosed following the discovery of microscopic hematuria (Zimmerman and associates)

A completely accurate tabulation of the malignant pheochromocytomas thus far reported is difficult because some of them developed metastases after first being reported benign, others, reported as malignant, do not fulfill the above enumerated criteria, and some have been reported several times in different papers without case identification On the basis of the available literature, we have collected 56 malignant pheochromocytomas

While the prognosis of patients with invasion and metastases is grave, one case of metastasis to a rib with removal of the primary adrenal focus as well as the metastatic site has survived at least two years (Remine and associates) Followups show no return of pressor activity Complete surgical extirpation is the treatment of choice Deep x-ray has been little tried, but where used has not altered the progressive course of the disease (Schwarzhoff) Owing to the great similarity histologically between malignant and benign pheochromocytoma cells and the lack of correlation between the primary cell type and metastases, it would be well to consider any pheochromocytoma postoperatively, a possible malignant one until time proves otherwise Metastatic involvement has been seen as late as seven and a half years after removal of a "benign" pheochromocytoma (Console and associates) Following the surgical removal of a tumor, the return of pressor activity, responsive to regitine, may indicate either another benign focus or functioning metastases

SUMMARY

A case of malignant pheochromocytoma weighing 1300 gm is reported exhibiting renal invasion with adherence to the stomach and aorta in a patient who possessed the voluntary ability to elevate his blood pressure at will, by lateral flexion of the vertebral column

The incidence of malignant pheochromocytomas is 8 to 11 per cent among large series and 30 per cent in bilateral tumors

Pressor effect, either sustained or paroxysmal, may or may not be present in malignant pheochromocytomas

The diagnosis of malignancy should be based not on cellular pathology alone but rather on evidence of invasion or metastasis

Pheochromocytomas which are diagnosed as benign may later show metastases

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SOLITARY ADENOMA OF THE KIDNEY

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Adenomas of the kidney occur as a solitary tumor of an otherwise normal kidney and as single or multiple adenomas of an arteriosclerotic kidney. The solitary adenoma develops in younger individuals while those in arteriosclerotic kidneys are in adults beyond 40 and may be small, multiple, and resemble miliary tubercles. They originate from renal tubules. Opinions concerning the pathogenesis and relationship of cortical adenomas to arteriosclerotic kidneys have been reviewed by Twiss.[1]

Adenomas are gray to yellow, sometimes hemorrhagic, and are in the cortex, flat or bulging beneath the capsule. In the group studied by Trinkle[2] they ranged from those microscopic in size up to 4 cm. in diameter. Childs and Waterfall[3] described a tubular adenoma 29 by 18 by 12 cm. which together with the kidney weighed 2470 gm. Bailey and Harrison[4] observed an adenoma at autopsy that weighed 3700 gm.

Histologically, adenomas are papillary, alveolar or tubular. The incidence of the three types in published reports depends upon the criteria used for classification. Papillary (cyst) adenomas have branched stalks of vascular stroma covered by epithelium which protrude into the cyst. The epithelial cells are arranged about crevices to form tubules or gland-like structures and the cytoplasm is usually dense. According to Trinkle, large tubular adenomas described in the literature frequently have papillary tissues which suggest an origin in a papillary adenoma. Trinkle also described hydropic degeneration of the cells in papillary cyst adenomas. These groups of large cells with a clear cytoplasm further complicate the classification of the tumors. Some papillary adenomas have large cells with an abundant acidophilic cytoplasm and small nuclei.[5] Adenomas of the arteriosclerotic kidney frequently are papillary.

Alveolar adenomas are rare. They have large polyhedral cells arranged in solid groups about the size of a convoluted tubule and resemble hypernephromas. According to Morris[6] the stroma of these encapsulated tumors is in thick bands of fibrous tissue with smooth muscle fibers. These bands extend from the inner

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surface of the capsule and form large alveolar spaces which with further subdivision extend as slender partitions, separating small secondary alveoli Large congenital adenomas may have an alveolar structure[7] Bell and Johnston[8] in 1890 surgically removed an alveolar adenoma from a 39-year-old woman and described the histologic structure in detail The delicate reticular fibrous stroma enclosed round or oval alveolar spaces 0 05 mm to 0 5 mm in diameter These contained 3 to 20 large polygonal cells averaging 15 to 20 μ in diameter, cytoplasm was clear and contained droplets of fat A necropsy revealed no metastases

Tubular adenomas have elongated and irregular canals lined by small cells free from fat and consisting chiefly of nuclei The *stroma is abundant and vascular* and the peripheral portion of the tumor may pass into surrounding renal tubules[7] This form coincides with the canalicular type described by Morris[6] as a mimicry of renal tubules completely developed or towards complete development

Transitions from adenoma to carcinoma (hypernephroid) have been described[2] and indeed, a distinction between benign and cancerous renal tumors can be difficult *Multiple adenomas of arteriosclerotic kidneys, according to* Bell,[9] *do* not become cancerous However, with solitary tumors the distinction between adenoma and adenocarcinoma is somewhat arbitrary His study disclosed that tumors less than 5 cm in diameter metastasize infrequently while larger ones may The histologic structure of the tumors does not afford a reliable distinction between adenoma and carcinoma Dukes[10] also noted that histologically benign adenomas may be cancerous and even after removal may recur He regards all *adenomas larger than two inches in diameter as potentially malignant*

Histologic features which indicate that these tumors are benign are mentioned by Creevy[11] These include small nuclei, absence of nucleoli and mitotic figures, distinct cell margins, and orderly arrangement of cells Kozoll and Kirshbaum[12] found that tumors considered benign in histologic structure may produce metastases and they stated that autopsy verification is required before a tumor can be accepted as benign

The *incidence of renal adenomas in necropsy statistics* ranges between 0 081 and 3 866 per cent according to Uys[13] Relatively few cause symptoms leading to nephrectomy Childs and Waterfall[2] in 1953 collected 33 reports of renal adenoma removed surgically and described two more Watts[14] reported another in 1955

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Partial nephrectomy was done in at least three patients[14 16] Cristol, Bothe and Grotzinger[17] reviewed 49 reports of renal adenoma producing symptoms and added an additional case in 1950 but not all were removed surgically

Clinically, adenomas of the kidney are difficult to differentiate from other renal tumors According to Jacobs and Salwen,[18] the most constant sign is a mass Hematuria was less constant and pain, when present, was attributed to the passage of blood clots from the renal pelvis, pressure on the diaphragm, displacement of the bowel or spleen, or pressure upon pelvic structures Radiographic studies may demonstrate a soft tissue mass and urography a smooth distortion of the renal pelvis with marked elongation of one or more of the calyces[4] Distortion of a calyx may be slight and easily overlooked, as reported by Creevy Barium enema may disclose displacement of the colon[4]

CASE REPORT

A 65-year-old white female nurse was admitted to St Luke's Hospital on April 18, 1951 complaining of diffuse colicky pain in the abdomen for several months The pain was sometimes relieved by a laxative and finally localized in the left side of the abdomen She had loose stools for several years, mucus was present but no blood On physical examination the pulse was 80 and the blood pressure 170/90 mm of mercury There was spasm of the left rectus muscle and tenderness to deep palpation in the left para-umbilical region where there was a vague mass about 8 to 10 cm in diameter Roentgen films of the abdomen disclosed that the right kidney was not enlarged and that the left was poorly visualized Barium enema revealed diverticula of the rectosigmoid and distal colon and some scarring Incomplete filling of the large bowel occurred The Kahn and VDRL tests of the serum were negative, the blood nonprotein nitrogen was 35 mg per cent and the sugar 114 mg per cent, the erythrocyte sedimentation rate was 55 mm in 60 minutes, the blood had 3,820,000 red cells and 7,350 white cells per cu mm , the hemoglobin was 10 8 gm per cent and a differential leukocytic count was within normal limits The straw colored urine had a pH of 5 0, no albumin or sugar No erythrocytes were found in the sediment

She was admitted again on September 4, 1956 because of (abdominal) soreness and occasional sharp pain attributed to diverticulitis of the colon Her pulse was 64 and the blood pressure was 186/100 mm of Hg There was a diffuse tenderness of the abdomen about the umbilicus and an indefinite mass was palpated in the region of the left kidney Roentgen films revealed a large, soft, ovoid tissue mass in the left upper quadrant of the abdomen The mass was partially over the psoas muscle shadow, closely approximated the kidney shadow and displaced the colon to the left A barium enema revealed many diverticula of the colon A comparison with films taken during the previous hospital stay disclosed that the soft tissue

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surface of the capsule and form large alveolar spaces which with further subdivision extend as slender partitions, separating small secondary alveoli Large congenital adenomas may have an alveolar structure[7] Bell and Johnston[8] in 1890 surgically removed an alveolar adenoma from a 39-year-old woman and described the histologic structure in detail The delicate reticular fibrous stroma enclosed round or oval alveolar spaces 0 05 mm to 0 5 mm in diameter These contained 3 to 20 large polygonal cells averaging 15 to 20 μ in diameter, cytoplasm was clear and contained droplets of fat A necropsy revealed no metastases

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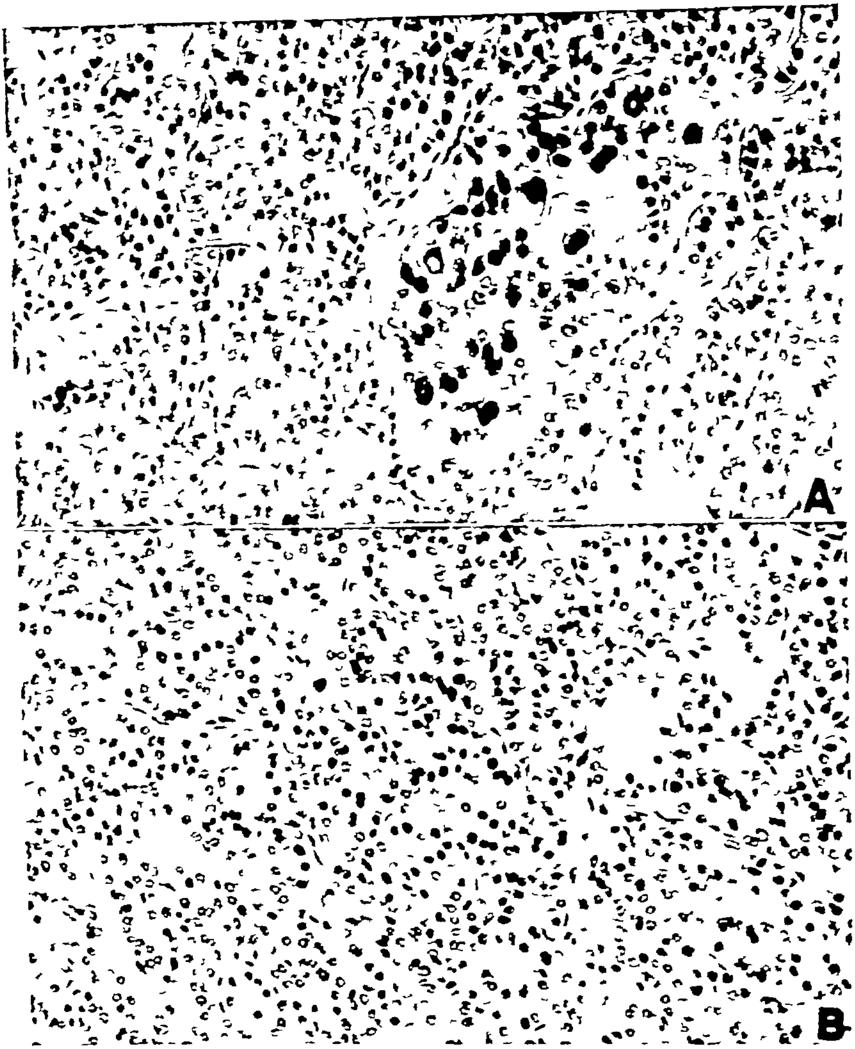

Fig 2 Photomicrographs illustrate (A) group of large cells and (B) general structure of adenoma of kidney

The patient recovered from the operation, gained weight, became symptom free and was well 8 months later when last examined

COMMENT

The presence of a palpable mass in the region of the left kidney associated with changes in roentgen films led to the surgical removal of this tumor An evaluation of the abdominal pain was complicated by the presence of diverticula of the bowel as shown by roentgen films As in the case described by Creevy,[11] the significance of the slight changes in the films was not fully appreciated In that case, four pyelograms showed partial obliteration of an upper minor calyx Surgical decapsulation of the kidney gave temporary relief of pain and six months mass on the left side was present previously and had increased only slightly in size An intravenous pyelogram demonstrated a 12 by 14 cm mass extending from the lower pole of the left kidney The mass had faint densities (calcium) and the lower portion of the kidney was obscured or obliterated by the mass The inferior calyces on the left were distorted laterally and medially and appeared to override the mass

The left kidney was removed surgically September 18, 1956 It had a solid tumor in the lower pole without extension into the renal vein or renal fossa

The surgically excised kidney with a tumor 11 by 8 by 4 5 cm in the lower pole weighed 383 gm (fig 1) The renal capsule continued over the external surface of the tumor and only a poorly defined capsule separated the tumor from the kidney Surfaces made by cutting the tumor were dark brown mottled with tan and gray in which were scattered light gray-yellow regions 1 to 8 mm in diameter Histologically (fig 2) the tumor consisted of solid cords of medium-sized cells with an abundant, finely granular acidophilic cytoplasm and small, oval nuclei The cords were compactly arranged or occasionally separated by edematous fibrillar tissue Rarely the tissues had tubule-like structures with similar cuboidal or columnar cells arranged about lumens containing acidophilic granular precipitates Although most cells were uniform in size, a few were large with multilobular nuclei Only occasional deposits of sudanophilic fat were found in large mononuclear cells in regions of cellular debris

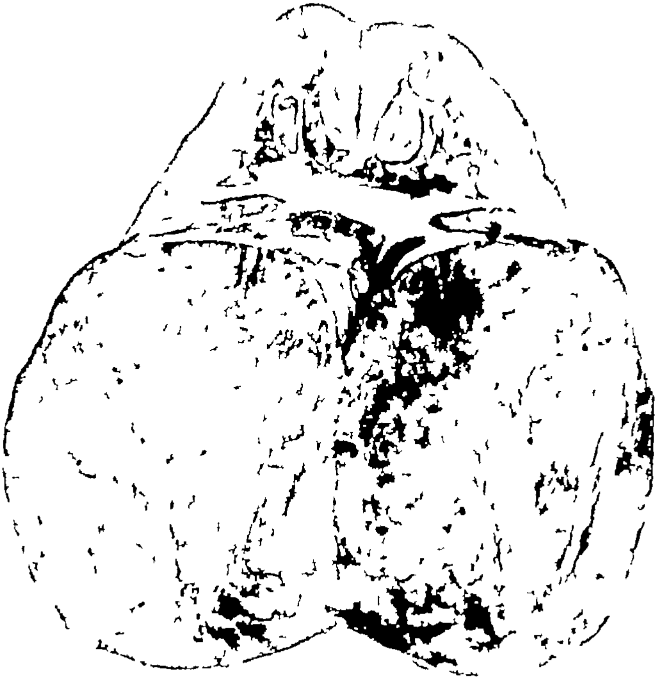

FIG 1 Gross appearance of adenoma of kidney

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AN ANTERIOR EXTRAPERITONEAL INCISION FOR KIDNEY SURGERY

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Ample surgical exposure of the kidney and upper ureter can be provided by an anterior extraperitoneal incision performed with the patient in the supine position on the operating table Twenty such procedures have been performed by the author during the past two years in an attempt to provide a more comfortable postoperative period for his patients and to explore the possibilities of the incision Fortunately, by chance alone, a wide variety of lesions were treated by definitive surgery, and the operation has been put to a variety of tests The experience has been advantageous for both surgeon and patient, and it is hoped that this report will encourage others to evaluate the procedure

POSITION OF THE PATIENT

The aim of this approach is to provide as broad an exposure as possible in the triangle created by rectus muscle, rib cage, and the line connecting the tip of the eleventh or twelfth rib with the rectus, and at the same time to allow the intraperitoneal viscera to fall away from the operative site by gravity This is accomplished, as shown in figure 1, by placing the patient supine on the slightly overextended operating table with a sandbag beneath the ipsilateral sacroiliac articulation The ipsilateral arm and shoulder may lie flat, or be placed in rotation on an arm rest (fig 1, *A*) when the surgeon suspects that he might wish to carry the incision more posteriorly through or between the beds of the ribs In either case respiratory exchange is not limited

THE INCISION

The incision has been made most commonly from the tip of the eleventh rib to a point over the ipsilateral rectus muscle, about midway between the xiphoid process and the umbilicus However, the actual line of incision may vary considerably depending upon the position of the kidney or type of pathologic lesion In general it should be placed over the anticipated position of the renal pedicle The line of incision is usually horizontal, but the higher the suspected position of the pedicle indicated by the pyelogram, the more the anterior extent of the incision should curve cranially The external oblique muscle is transected in the line of skin incision, and in this plane the incision is usually carried through the anterior rectus sheath to the midline Occasionally, the exposure is so broad, due to anatomic variations, that the rectus sheath is not entered The internal oblique is split or transected (fig 2, *A*) depending on the breadth of exposure desired and the line of the muscle bundles In this series it was possible to use a muscle-splitting incision 50 per cent of the time, although no special attempt was

Read at annual meeting of Western Section of American Urological Association, Seattle Wash , May 27-30, 1957 later nephrectomy demonstrated a 3 cm tumor that compressed the upper calyx In the patient of this report, comparison of 1951 x-rays with those of 1956 indicated that the tumor changed only slightly in size during this time suggesting that it was slow in growth and was present for several years

SUMMARY

A renal adenoma, barely palpable, was accompanied by abdominal pain and some tenderness The adenoma appeared in roentgen films as a soft tissue mass extending from the lower pole of the left kidney It increased in size slightly during five years It had faint calcific densities and its growth distorted the inferior calyces The left kidney with the tumor was removed surgically

The pathology and clinical features of renal adenomas are briefly reviewed

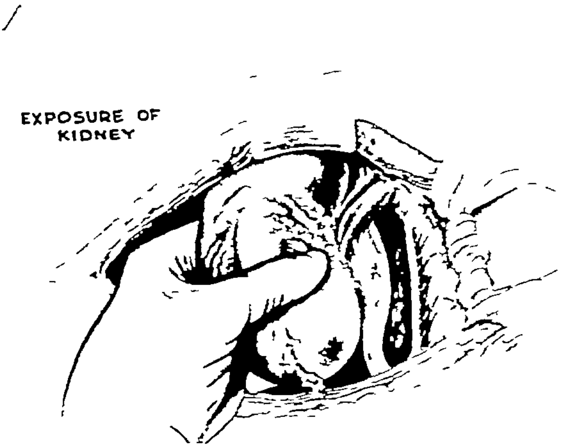


FIG 3

At this point in the operation the familiar motions of the lumbar approach are used The dissecting hand should sweep far posteriorly to the lateral edge of the psoas muscle before the transversalis fascia is sharply entered This is easily done The peritoneum can then be displaced forward in the usual manner The anterior surface of the kidney and Gerota's fascia are then exposed and the operation may then proceed in the classic manner The pedicle may be either sharply or bluntly dissected out, the upper ureter and extrarenal pelvis quickly and easily identified and isolated (fig 3) This came as a surprise to me, for my belief had been that these structures must always be approached from the rear because they lie in a plane behind the pedicle Retraction of the peritoneum alone is necessary as one works on these structures since the kidney lies undisturbed in its bed and these tissue planes are left untouched The common problem attacked at the ureteropelvic area is stone, and as little actual dissection as possible of the kidney itself is desirable in the event of future operative treatment of calculi

Exposure of the adherent or enlarged upper pole of the kidney may be difficult On the right side the peritoneum fans out under the diaphragm and over the liver so that it tends to arch tensely over the upper pole and to limit vision If added exposure is mandatory this thin arch may be split A laparotomy tape is then placed in the notch thus created, and the intraperitoneal structures left undisturbed Avoidance of handling of the small bowel seems wise in minimizing postoperative ileus Although the kidney normally lies highest on the left, the peritoneum is less of a problem there and is easily stripped medially Upper pole limitations remain much the same as with the lumbar approach

Closure is carried out in well-defined layers, this is often rapid in cases in which muscle splitting was possible Soft rubber drains are brought out through the posterior angle of the incision or through a posterior stab wound When muscles are well-developed and liable to close off the drainage tract, an additional firm rubber drain is placed through the muscle layers alone A posterior stab wound may be used when a nephrostomy tube and splints are required to support the kidney permanently in the desired position, as after a plastic operation on the ureteropelvic junction

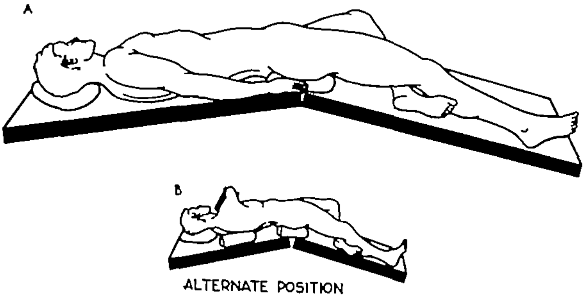


FIG 1

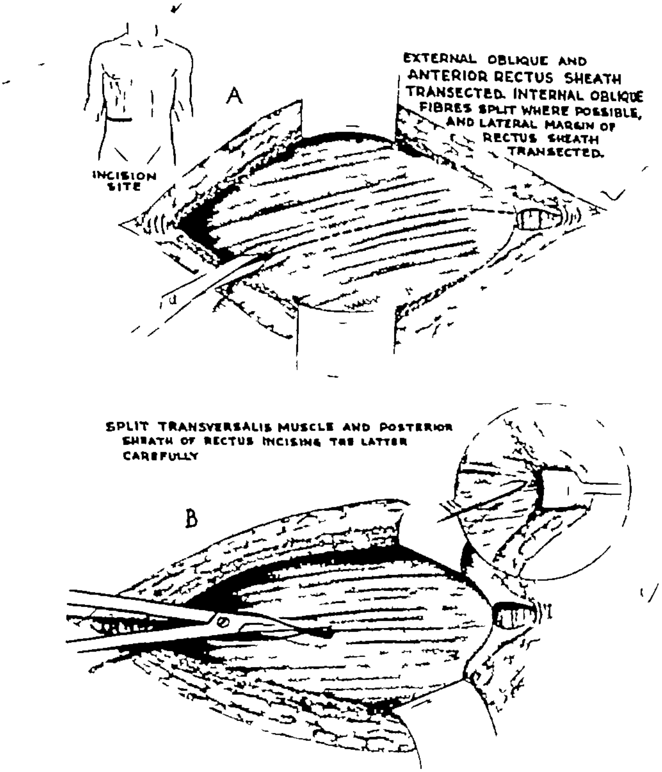

INCISION SITE
A
EXTERNAL OBLIQUE AND ANTERIOR RECTUS SHEATH TRANSECTED. INTERNAL OBLIQUE FIBRES SPLIT WHERE POSSIBLE, AND LATERAL MARGIN OF RECTUS SHEATH TRANSECTED.
SPLIT TRANSVERSALIS MUSCLE AND POSTERIOR SHEATH OF RECTUS INCISING THE LATTER CAREFULLY
B

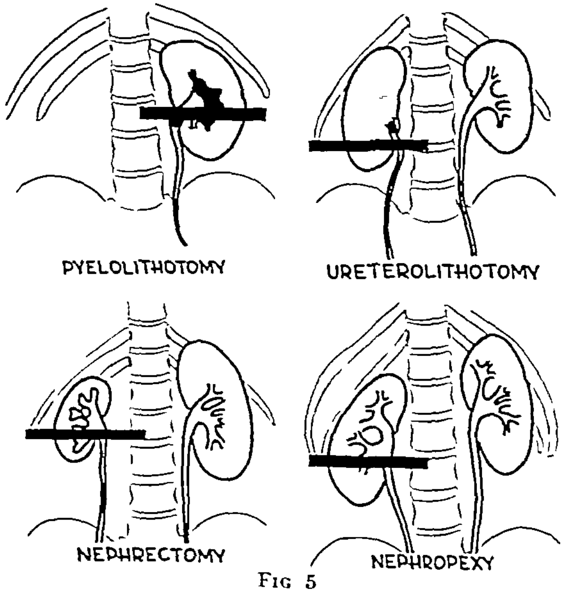
FIG 2

made to accomplish this as being desirable The transversus muscle is always split and the condensation of fascia at the lateral margin of the rectus is carefully incised (fig 2, *B*) The latter step is of the greatest importance in freeing the medial structures It is then wise to incise a short distance through the posterior sheath, this should be done gently however to avoid entering peritoneum which is usually adherent at this point Avoiding the neurovascular bundles appears to be less of a problem than with the lumbar incisions The tenth nerve is rarely encountered The eleventh and twelfth nerves lie below the incision, the eleventh is encountered 50 per cent of the time, and the twelfth is well out of the line of closure anterior approach in conditions in which extensive scarring was expected and encountered

RESULTS

Unusual operative difficulties were largely limited to those produced by perinephric scarring of an enlarged upper pole of the kidney However, in all cases it was possible to isolate the renal pedicle, usually with sharp dissection in combination with the educated index finger, before aggressively manipulating or freeing of the upper pole In the cases of suspected neoplasm the pedicle was occluded before manipulation of any part of the kidney With cysts, the beds could be visualized and excision completed with neoplasm, nephrectomy was completed In a multicystic kidney when it was difficult to bring the cystic area completely into view cysts of the upper pole were opened by touch alone However, theoretically it seemed wise not to traumatize the opposite enlarged kidney by flexion of the table in the lateral position and the anterior incision was repeated

Two major hemorrhages from the pedicle were due to trauma to large aberrant vessels The incision was then extended to the midline through the ipsilateral rectus and a broad exposure of the vena cava and its tributaries achieved This allowed repair of the vessel in one case, planned nephrectomy was carried out in the other The one nephropexy in the series presented a real problem in fixation since I had been trained to utilize upper pole fixation It was too difficult to place these sutures, however, and ribbon gut was used in the midportion and lower pole A Deming sling was then added It was a pleasure to have a neuritis-free course for this "painful kidney" patient



PYELOLITHOTOMY

URETEROLITHOTOMY

NEPHRECTOMY

NEPHROPEXY

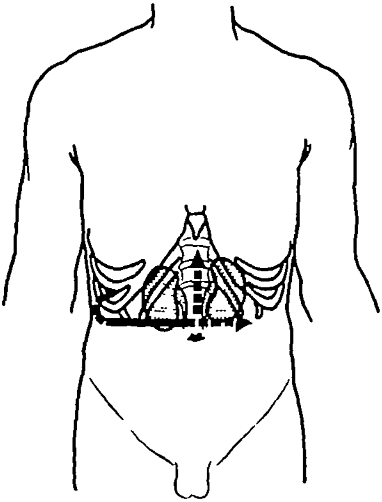
FIG 5

METHODS OF INCREASING EXPOSURE

In figure 4 are shown the lines of possible extensions of the incision to meet unusual problems Transection of one or both recti may be carried out by continuation transversely When both muscles are sectioned the peritoneal cavity is necessarily entered and the operation becomes a transperitoneal one Division of the ipsilateral rectus allows added exposure of the large vessels, vena cava and aorta Such an extension was necessary in two cases in order to control and repair lacerations of aberrant blood vessels The midline extension superiorly to the xiphoid was not used in this series, it does provide preservation of nerve trunks however, although it adds the risk of postoperative hernia, and should be kept in mind as a possible aid in the rare case

Although conversion of the anterior incision to a semi-lumbar incision by extension posteriorly would seem logical to create added exposure, this has not seemed to be the case in the conditions met thus far As the surgeon explores the possibilities of the anterior approach, however, it is comforting to know that by hyperextending the table and enlarging the incision posteriorly, he can return to the familiar territory of the lumbar route

Nephro-ureterectomy is well handled by combining the basic incision with a lower quadrant incision, there is no need to move or reprepare the patient It was fortunate that in the first of such cases the supine operating position was mandatory because of problems of pulmonary ventilation and the danger of a tuberculous pulmonary spill A tuberculous pyoureter and pyonephrosis were removed without peritoneal contamination in average operating time The successful handling of this early problem encouraged further exploration of the



POSSIBLE INCISION EXTENSIONS

FIG 4

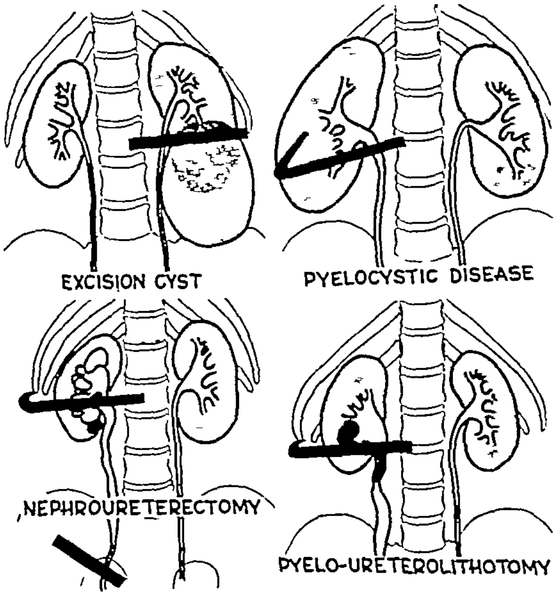


FIG 7

ing French medical journal of the day, however, the article is vague concerning his actual clinical experiences with this technique Exposure of the pedicle was then, as now, the advantage of this procedure, in addition to the extraperitoneal aspect Bazy was not concerned with possible advantages of the supine over the lateral flexed position, required by the lumbar approach in all its variations This incision then receded into oblivion for reasons about which we may only conjecture

Writing in 1957, rather than 1914, I believe that the classic "kidney position" is one that should be re-evaluated in terms of its effects on the patient and its necessity in operations upon the kidney Each urologist should have himself placed in this position with the table in flexion, without anesthesia, and then have the kidney bar raised Flexion alone is extremely painful and intolerable for more than several minutes Because of thoracic compression one's breath comes in gasps as he tells an associate to straighten the table Elevation of the kidney bar is immediately intolerable

How much then of postoperative pain with resulting immobility is in reality due to the incision itself and how much to stress, strain, and back sprain? The anesthesiologist[2] will warmly attest to his problems with patients' ventilation and circulation, problems he has been taught to consider necessary in surgery of the kidney The urologist remembers his patients' postoperative problems of atelectasis related to operative position and ventilation, as well as vascular and pulmonary complications related to immobility The elderly patient, and half of the patients of this series were in this age group, is surely the most vulnerable

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Case E H and Stiles J Effects of various surgical positions on vital capacity Anesthesiology 7 29–31 1946

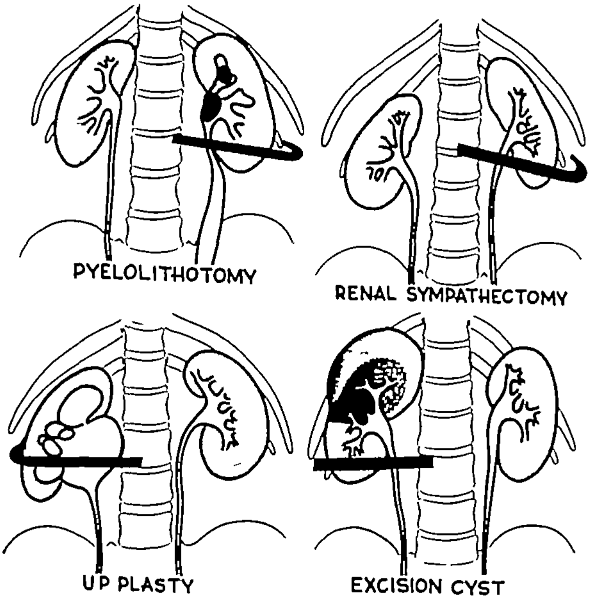

Fig 6

The early postoperative period has seemed less painful than that after the lumbar incision This must remain a clinical impression only However, the patients did seem to breath deeply with ease early on the operative day and to ambulate more enthusiastically on the first postoperative day Ileus and pulmonary-cardiovascular problems were absent No hernias have occurred up to the time this report was written

I have found that the long-term postoperative courses have been more satisfactory than after the lumbar incision Hypoesthesia in the distribution of the tenth and eleventh nerves was present in three patients for several of the early postoperative weeks, but there was no long-term distressing neuritis

DISCUSSION

Of 23 consecutive patients requiring operation of the kidney and upper ureter, 20 were operated upon by the anterior extraperitoneal route The first case was a carefully selected one of a patient with a small, low, atrophic kidney A modification of the classic lumbar incision was used, the incision was brought in front of the twelfth rib with the patient placed halfway between extreme flexion and the supine position The remaining 19 cases can be considered almost unselected, although a wide variety of pathologic lesions were present (figs 5–9) Of the three patients operated upon by the classic lumbar route with resection of the twelfth rib, one patient had massive hydronephrosis and two had staghorn calculi In retrospect, the hydronephrosis certainly, and the calculi perhaps, could have been operated upon as well from the front

This incision is not new In 1914, Bazy[1] described such an incision in the lead-

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[1] Bazy, L La néphrectomie sous péritonéale par incision antérieure transversale Presse méd , 22 186–188, 1914

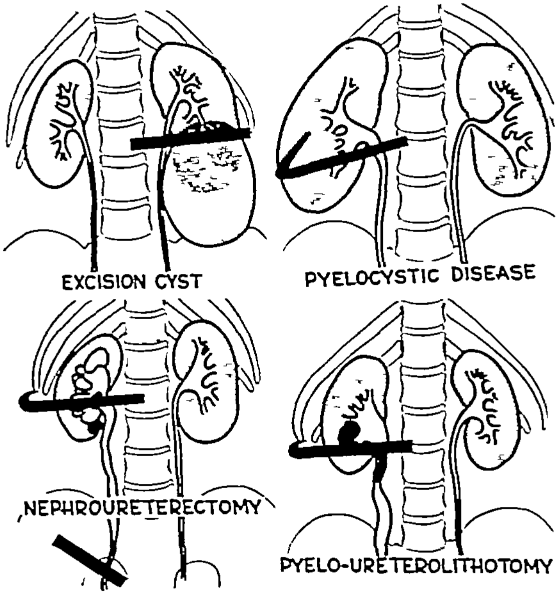

FIG 7

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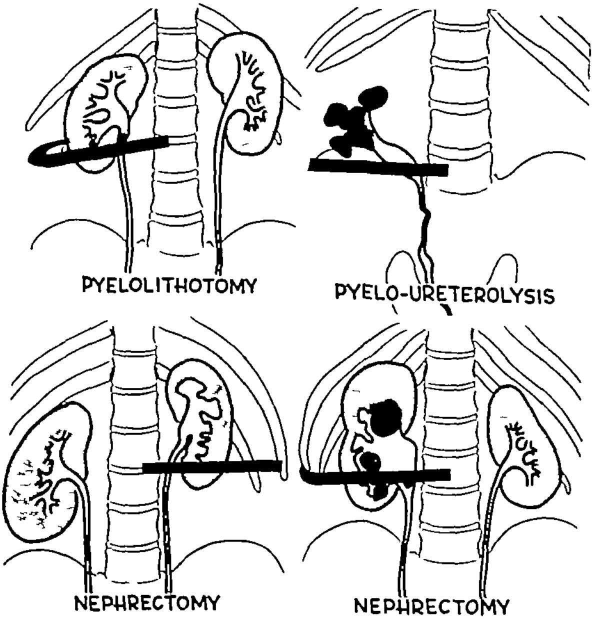

Fig 8

Perhaps the author's concern with these uncommon problems has been too great, but the anterior approach was devised primarily to eliminate the rigors of the lumbar approach that result from the patient's position, to remain distant from the twelfth nerve to the point of not unknowingly incorporating it in closing sutures, and to provide broad exposure of the renal pedicle

In 1950, Lich and Maurer[3] described a similar approach to the midureter, which was suggested by its accessibility during lumbar sympathectomy This technique possessed the advantages of broad ureteral exposure and the need for only one assistant This, too, has been my experience In addition, it is a constant surprise to find the renal pelvis readily visible when past teaching has suggested otherwise Thus, in a case (No 4) in which the patient was anuric for 72 hours due to an impacted section of staghorn calculus at the ureteropelvic junction in a solitary kidney, a short anterior incision allowed ample exposure and decompression with a T tube The kidney was left undisturbed permitting easy exposure by the lumbar route three weeks later when the staghorn calculus was removed If upper ureteral stones are inadvertently lost in the renal pelvis, they can be easily located and recovered, and the incision extended if necessary

What limitations are there to this approach? Probably the obese patient would be operated upon much more easily with the classic incision through thinner lumbar walls The high-lying kidney, more or less fixed on upright films, may be reached best through an eleventh rib-bed approach The impression is that the lower lumbar incisions meet the same difficulties found with the anterior incision

[3] Maurer, J E Lich, R , Jr and Grant O A new approach for surgery of the middle third of the ureter J Urol , 61 744–748, 1949

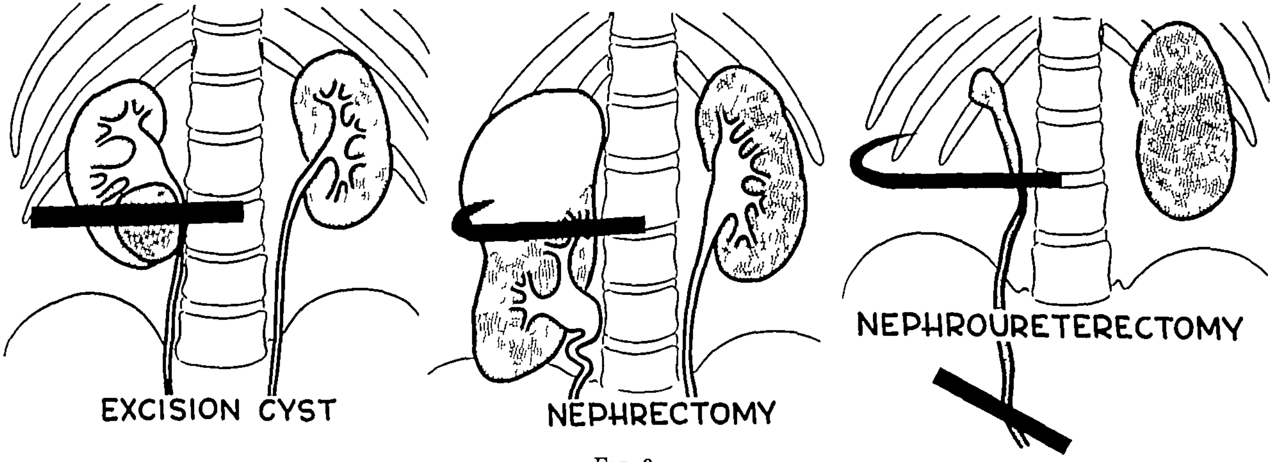

Fig 9

To many surgeons, active kidney infection is an indication for the lumbar approach, but it must be remembered that the danger of peritoneal spill is the same by either route, because the same tissue planes are entered

Hinman,[4] in his classic article, Nephrectomy, written in 1927, stated that "there is a certain charm in surgery of the kidney " I, too, have found this "certain charm" as familiarity with the anterior approach has increased, for with this and the lumbar incisions from which to choose, surgery can be planned to fit the patient

SUMMARY

A variety of surgical lesions of the kidney and ureter have been operated upon through an anterior extraperitoneal incision An attempt has been made to explore the possibilities of such an approach and to assess results over a two-year period The supine operating position offers more real advantages to the patient as compared to the flexed position demanded by the lumbar approach Exposure of the renal pedicle seems best by the anterior route The author has found that he has sacrificed nothing in operative safety by moving forward the field of operative exposure and vision It is hoped that others will explore further the possibilities of using this approach as a routine one for surgery of the kidney

3031 Telegraph Hill, Berkeley, Calif

[4] Hinman, F Nephrectomy Surg , Gynec & Obst 45 347–358 1927

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NEEDLE BIOPSY OF THE KIDNEY

A. WAITE BOHNE, ROBERT C. ACKLES, DALE R. DREW AND KENNETH L. URWILLER

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Needle biopsy of the kidney, although a relatively new procedure, is being used rather extensively in this country and Europe as an aid in the diagnosis of renal disease. The procedure was pioneered by Iversen and Brun[1] beginning in 1949. Subsequently several excellent reviews dealing with this problem, and refinements of the technique, have been published by Kark and associates,[2-5] and Parrish and Howe.[6] The original work done by Iversen and Brun was carried out with the patients in the sitting position and using an Iversen liver biopsy needle. Parrish and Howe varied this only in the use of a Turkel needle. The method of Kark with the patient in the prone position using a Vim-Silverman needle seems to us the superior method, and it is this technique which we are using at present.

INDICATIONS AND CONTRAINDICATIONS

There are certainly some patients on the urological service in whom an exact picture of the renal histology might alter definitive therapy. However, in the main, we have not used renal biopsy in the preoperative and postoperative evaluation of our surgical patients, but have rather depended on other time-honored tests for our evaluation. It has been our practice to use renal biopsy as an aid to our medical colleagues in attempting to further elucidate certain clinical problems which may have a renal etiology. In general we carry out these biopsies on any co-operative patient with probable renal disease. This might include diabetic patients with evidence of nephropathy, patients with chronic glomerulonephritis, severe hypertensives, a suspected diagnosis of lupus erythematosis, various degrees of nephrosis and a group of patients in whom the syndrome of "bacterial nephritis" may be suspected. We do not do biopsies on patients with a confirmed bleeding tendency, those with a solitary kidney, those who have a suspected renal neoplasm or tuberculosis, or those patients who are un-cooperative.

Read at annual meeting of North Central Section of American Urological Association, Mackinac Island, Mich., August 29-31, 1957.

[1] Iversen, P. and Brun, C.: Aspiration biopsy of the kidney. Am. J. Med., 11: 324, 1951.

[2] Kark, R. M. and Muehrcke, R. C.: Biopsy of kidney in prone position. Lancet, 1: 1047, 1954.

[3] Muehrcke, R. C., Kark, R. M. and Pirani, C. L.: Biopsy of the kidney in the diagnosis and management of renal disease. New Eng. J. Med., 253: 537, 1955.

[4] Kark, R. M., Muehrcke, R. C., Pirani, C. L. and Pollak, V. E.: The clinical value of renal biopsy. Ann. Int. Med., 43: 807, 1955.

[5] Kark, R. M., Pollak, V. E., Soothill, J. F., Pirani, C. L. and Muehrcke, R. C.: Simple tests of renal function in health and disease. I. A reappraisal of their value in the light of serial renal biopsies. Arch. Int. Med., 99: 176, 1957.

[6] Parrish, A. E. and Howe, J. S.: Needle biopsy as an aid in diagnosis of renal disease. J. Lab. and Clin. Med., 42: 152, 1953.

TECHNIQUE

The patient is questioned regarding any bleeding tendency If there is any question of this an evaluation of bleeding and clotting time and prothrombin level is made The meal immediately preceding the biopsy is omitted and the patient is given seconal gr 1½ about one-half hour prior to the procedure The patient's blood is typed and cross-matched and 500 cc are available at the time of biopsy An intravenous or retrograde pyelogram has been made prior to biopsy for proper localization of the kidney We prefer to use the right kidney thus precluding any possible injury to the spleen The patient is placed in the prone position on a stretcher A sand bag is placed under the abdomen at the renal level Before preparing the back with antiseptic solution, the area from which the biopsy is to be taken is localized This is done with frequent reference to the pyelogram In the normal instance, this is ½–1 cm lateral to the sacrospinalis and about 1 cm below the twelfth rib in the apex of the triangle formed by the sacrospinalis and the twelfth rib Under sterile conditions the skin and subcutaneous tissues are anesthetized by means of 2 per cent procaine With the patient

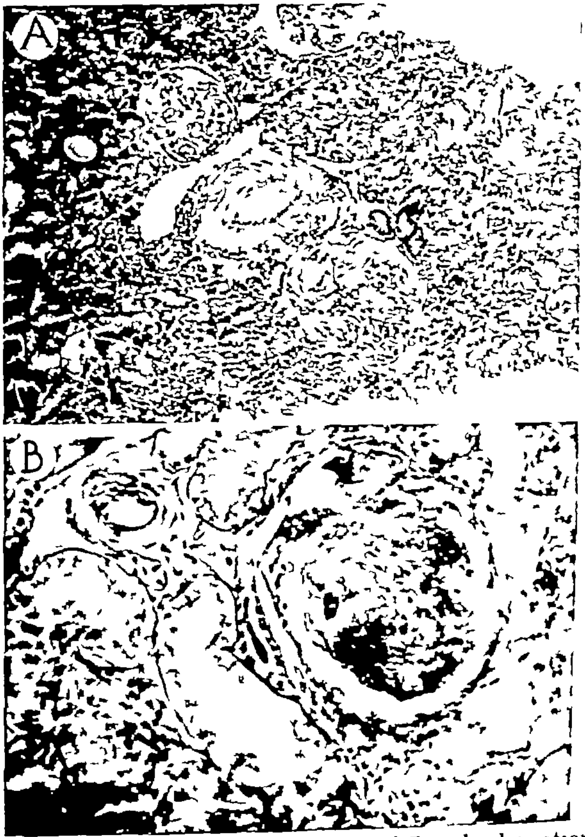

Fig 1 Arteriosclerosis of kidney A, ×160 B, note diffuse hyalinization of glomerulus ×420

in full inspiration and holding his breath we introduce a No 20 spinal needle to the region of the kidney, holding the needle vertically in a plane perpendicular to the flank As the kidney is entered a slight resistance is usually felt The patient is now instructed to breathe slowly at normal depth If the needle is in the kidney, a characteristic motion of the needle is seen, the hub moving in a wide arc toward the head on inspiration, and toward the buttocks on expiration The depth of penetration is measured and the needle removed, infiltrating a small amount of procaine along the path of removal A standard Vim-Silverman needle (size 14 G) is next introduced to the appropriate depth along this path with the patient in inspiration The patient is again asked to breath normally, and the swing of the needle observed The obturator is now removed, the sheath withdrawn approximately 1 cm to the cortical area, and the biopsy split needle introduced until resistance is felt This inner needle is then introduced into the kidney with a firm, thrusting motion The sheath is rotated down over the inner needle, thus impinging the tissue, and the needle removed A firm dressing is applied to the biopsy site and the patient allowed to remain with sand bag in place for one-half hour Blood pressure and pulse recordings are checked fre-

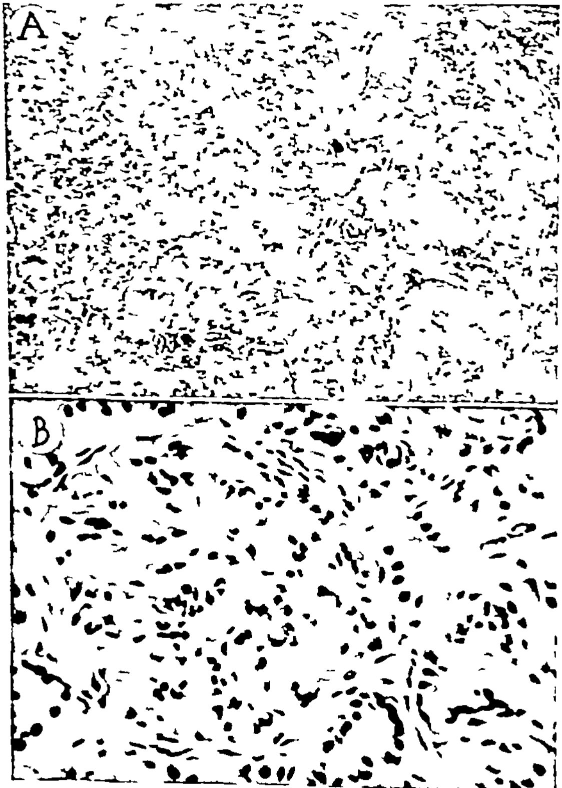

FIG 2 Acute membranous glomerulonephritis A ×170 *B* note diffuse thickening of capillary and basement membrane ×540

quently after the biopsy has been obtained. The patient is instructed to remain flat in bed for 24 hours and all voided urine is examined microscopically for the next 24 hours. By this method we usually obtain a specimen about 1 cm in length and 1 mm in diameter. This specimen may be sent in formaldehyde for microscopic section and in sterile culture tubes for tissue culture

RESULTS

In the past [illegible] months we have performed 30 biopsies In 23 we have obtained renal tissue, [illegible] per cent, which compares favorably with figures of Iversen who reports [illegible] per cent success, Kark who reports 93 per cent success, and Schw[illegible] who reports [illegible] per cent success In the 23 successful renal biopsies which we have performed, the clinical impression has been confirmed in 10 cases In [illegible] other [illegible] successful biopsies, the pathological diagnosis has differed from the clinical impression. In both groups the further clinical management of the patient has been aided by the knowledge gained In the three remaining successful biopsies the pathological findings were inconclusive Figures 1 and 2 indicate representative needle biopsies obtained

DISCUSSION

We have experienced very little in the way of complications following this procedure. In all cases we have noted microscopic hematuria, and in three cases gross hematuria, but no instance of retroperitoneal hemorrhage has occurred Complications which have been reported or anticipated include retroperitoneal hemorrhage, perforation of an intra-abdominal viscus, dissemination of a malignant or infectious process, or perirenal infection We believe that the patient should be hospitalized for this procedure, mainly for adequate post-biopsy follow-up. This is certainly a relatively safe procedure if done with adequate knowledge of renal anatomy and realization of possible complications

SUMMARY

We believe that needle biopsy of the kidney is a valuable procedure, which may either change or confirm clinical impressions It is a safe procedure if proper precautions are taken The results compare favorably with biopsies obtained with [illegible] [illegible] systems carried out in the routine manner

[illegible] G W and Hodges, C V Aspiration of the kidney J.A.M.A., 159 1198 [illegible]

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GIANT POLYP OF URETER

T LEON HOWARD

In the practice of a urologist who has confined himself to this specialty for the past 50 years, it seems logical that "rare" entities of the ureter should have been observed not once, but many times From the ninth verse of the first chapter of Ecclesiastes is inscribed a very pertinent notation "There is no new thing under the sun," which makes one realize that "the more you think you know the more you had better listen "

With such evident facts before me, I am dubious about presenting this giant polyp of the ureter even as a rarity, much less as one among the first 25 to be reported In all the years of viewing unusual renal and ureteral conditions, I have only seen one polypoid growth in the upper urinary tract and that was in October 1956 at the meeting of the South Central Section in Mexico City This case was presented by Drs Herbert E Isaacks and Dolphus E Compere of Fort Worth, Texas It was so well presented that it merited honorable mention for the second best case of the "Problem Hour " The polyp was located in the right renal pelvis, was bifid in character, and acted as a valve to obstruct the ureteropelvic outlet with destruction of the kidney A personal communication from Capt W M Silliphant, director of the Institute of Pathology in Washington, D C to Dr Paul K Hamilton, Jr , pathologist at Mercy Hospital, Denver states "As far as we can determine there are only two similar cases of reactive ureteral polyps in the files at the Armed Forces Institute of Pathology "

In UROLOGY, edited by Campbell, is shown a case of Dr Francis C Regan of Rochester, N Y which, in many respects, is quite similar to ours Dr Regan writes that he has never published the history of this patient Dr Campbell records 7 cases of true ureteral polyps in the chapter on Tumors of the Urogenital System

In 1957 Twinem presented a paper on Primary Tumors of the Ureter in which no mention of polypoid growths is made In 1932, Melicow and Findlay collected 28 proven cases of benign ureteral tumors, four of which were fibrous in consistency and the rest papillomatous Campbell's comment on this series is interesting for he states that 16 pathological terms were used in describing the types of tumor found in the Melicow and Findlay collection I should like to suggest that perhaps 16 different pathologists passed opinions on these specimens The lower ureter was the site of the growth in 75 per cent and hematuria was a cardinal sign in 75 per cent of these cases I wish to emphasize the fact that the patient whose case I am reporting did not seek medical aid for urinary symptoms but for persistent jaundice and rapid loss of weight

CASE REPORT

T S of Nebraska, a white gasoline station attendant aged 60 years, entered St Luke's Hospital, Denver on July 23, 1956 and was admitted to the service of Dr Fred Harper Both parents had died of cancer

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Read at annual meeting of Western Section of American Urological Association Seattle, Wash May 27-30 1957

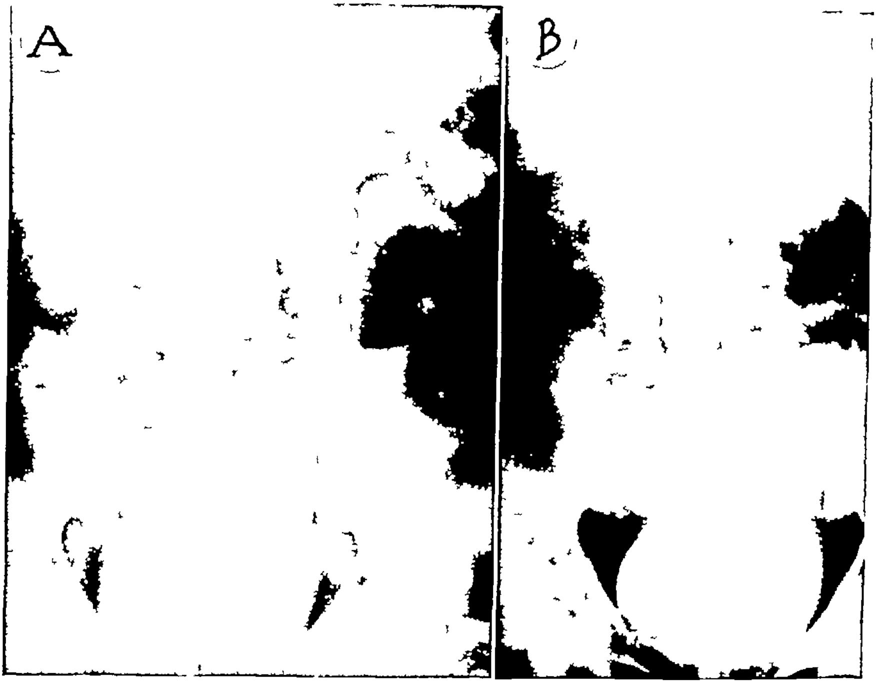

FIG 1 *A*, retrograde pyelogram, July 24, 1956 Normal left kidney, bulb catheter in lower right ureter and large filling defect *B*, two catheters in right ureter with shadows of calculi and spiral catheter encircling polyp, December 5, 1956

Only pertinent facts in the history will be cited In 1952 the patient had an attack of hematuria Under medication the bleeding ceased until May 20, 1956 when bright red blood appeared in a voided specimen for four days without subjective symptoms At the same time he became icteric In order to determine the cause of the hematuria, the family physician made an intravenous urogram which showed right hydronephrosis and a normal left renal pelvis In July 1956 the patient entered St Luke's Physical examination disclosed an enlarged liver The laboratory data were suggestive of biliary tract obstruction

Dr Emerson J Collier was responsible for the urological conclusions as he was called in consultation by Dr Harper at this time On July 24, 1956, Dr Collier, with the patient under a spinal anesthetic, made a retrograde pyelogram (fig 1, A) which revealed a normal left kidney, a bulb catheter in the lower right ureter and a large filling defect of the ureter on that side No stone shadows were seen When examination of the urinary tract study was completed, Dr Collier was of the opinion that the illness of the patient was probably caused by ureteral carcinoma and the jaundice secondary to metastatic liver involvement from the tumor

As the patient was steadily losing weight from probable malignant lesion in the liver, it was deemed justifiable to explore the area of the liver first Dr Harper performed an exploratory laparotomy on August 5, 1956 Little beyond an occluded common bile duct as it entered the bowel was found A T tube was placed in the duct for drainage The right kidney and the ureter were then palpated The kidney felt normal, but a large sausage-shaped mass was followed from just below the kidney pelvis to the region of the bladder It was deemed unwise to take sections from the mass

The patient was next seen on our service at Mercy Hospital, Denver on December 4, 1956 The bile duct T tube was still draining satisfactorily and a gain of 25 pounds in weight was admitted Jaundice had disappeared and the only complaint was burning on urination with, at times, a dark colored voided urine On December 5, 1956 my partner, Dr Henry Buchtel, introduced a Johnson's basket up the right ureter in an attempt to snare off a specimen for pathological study Failing in this he then passed two catheters up the right ureter and the radiologist's comment was as follows "A radiopaque catheter shows the distal end at the upper fold of the right kidney A second catheter extends to the level of the upper margin of the sacroiliac joint It is debatable whether these catheters are within the ureter If the catheters are within the ureter, the diagnosis is megaureter There are two calcified densities, one in the region of the right kidney area, the other in the lower portion of the right ureter The intrahepatic biliary system was delineated by an air contrast study" Figure 1, *B* shows two catheters in the right ureter described by the roentgenologist with stone shadows and a spiral catheter encircling the polyp The ureterogram was little different from that made by Dr Collier in July 1956, except that one catheter ascended in a spiral The stone shadows were not seen in the July 1956 roentgenograms but can be outlined in figure 1, *B* (the December 1956 ureterogram) It is easily understood why the roentgenologist was confused about the location of the catheters

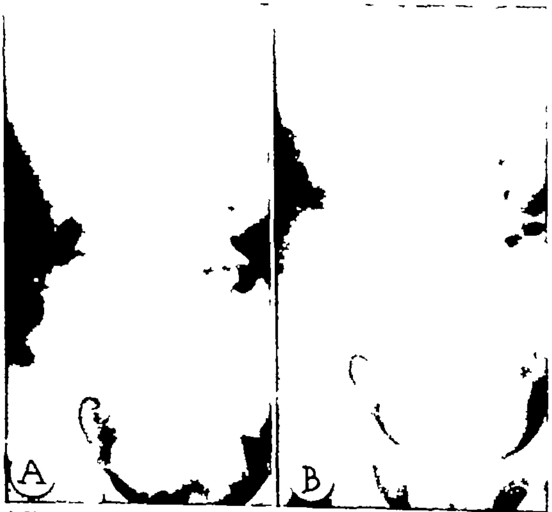

FIG 2 *A* third film in series of intravenous urograms at end of 30 minutes Dye appeared in good concentration in 5 minutes *B* 1 hour intravenous film Dye is beginning to leave renal pelvis

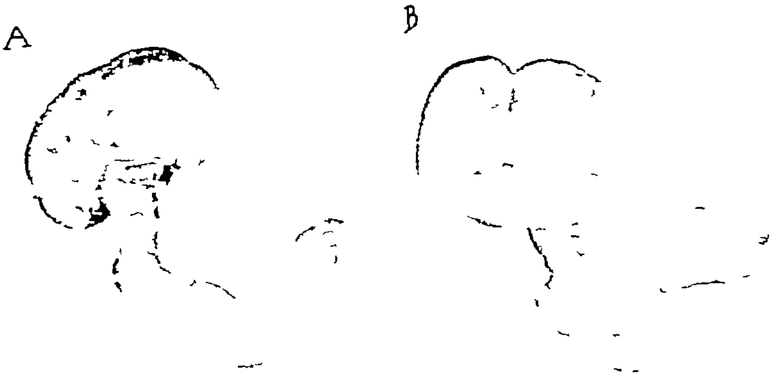

FIG 3 A, kidney and ureter intact B, kidney and ureter opened Note small granuloma in kidney center and giant polyp delivered from ureteral cavity

slightly irregular, granulomatous focus with marked central necrosis surrounded by a dense area of hyalinized fibrous tissue In some areas epithelioid cells are present in a palisading formation A few ill defined giant cells are present One of the interlobular veins contains a thrombosis No evidence of malignancy is noted

"Stains for acid fast organisms and periodic acid Schiff stains for fungi reveal none to be present

"Diagnosis Ureteral polyp, granulomatous focus, cortex of kidney, hydroureter with marked smooth muscle hypertrophy "

Figure 3, A shows the kidney and ureter intact, figure 3, *B*, after the kidney and ureter had been opened Note the small granulomatous focus in the center of the kidney and the giant polyp that was delivered from the ureteral cavity

COMMENT

According to Col James E Ash, "the development of polyps is largely a matter of vasomotor reaction and mechanics, the result of repeated and chronic attacks of inflammation of the mucosa " The microscopic findings in the polyps of the nose and those of the urinary tract are quite similar

Are we in the future going to find an increase in ureteral polyps? Such is possible, for one of the causes of nasal polypoid growths has been ascribed to an allergic background and each year the human race is being exposed to more antigens by the multitude of drugs that we are so indiscriminately prescribing Consequently, the question should be answered in the affirmative, for mucosal tissues are changed by repeated allergic reactions which are conducive to infection This is confirmatory of Col Ash's opinion as to the cause of these polyps

Had the patient not suffered jaundice and weight loss but sought relief from his urinary symptoms alone, I am confident his right urinary tract, in all probability would have been saved

The most interesting of Dr Collier's July series of intravenous films are reproduced in figure 2 Figure 2, *A* is the third of the intravenous series at the end of 30 minutes The dye had appeared in good concentration in 5 minutes Figure 2, *B*, a one-hour film, showed the dye beginning to leave the renal pelvis Another film showed that the dye had reached the pedicle of the polyp at the end of one and a half hours Evidently the kidney pelvis was in a state of systole A two-hour upper ureterogram showed the ureter in diastole The next film, taken immediately afterward, showed a violent systolic contraction of the pelvis and ureter The lower segment of the ureter, as it neared the bladder, was filled for the first time

Operation was performed by Dr William Ivers and myself on December 7 No difficulty was encountered in securing exposure of the entire ureterorenal tract through a right lateral rectus incision that extended from the middle of Poupart's ligament to the tip of the twelfth rib, then transversely to insertion of this rib The ureter felt like a well-filled colon and, through this same incision, the renal pedicle was easily delineated The ureter was ligated near the bladder where it was of normal size and dissected to the kidney pelvis without difficulty as there were no ureteral adhesions The renal vessels were differentiated, tied separately, then cut The entire renoureteral system was removed intact

The patient left the hospital on December 16, nine days after surgery, and all attempts to get him to return have failed Through correspondence he states that he is in excellent health but still is wearing his common bile duct tube

Description of gross specimen (Dr Paul K Hamilton) "The specimen consists of the kidney and ureter The external surface of the kidney appears normal, and it measures 11 by 6 by 4 cm The ureteropelvic junction appears relatively normal, measuring 1 5 cm in width At a point 6 cm distal to the junction, the ureter enlarges into a fusiform mass that has a maximum diameter of 2 5 cm The wall of the ureter in this enlarged area has a distended appearance and an increased consistency Within the lumen of the ureter a greyish-yellow, soft mass is found which is attached to the ureter just below the ureteropelvic junction by a narrow pedicle measuring 7 mm in diameter The mass measures 10 by 3 cm The mass appears to consist of grey, soft, finger-like projections which are fused together in several areas Two small calculi are found, one distal to the pedicle of the tumor mass and one proximal The average diameter of these calculi is 5 mm

"A hemisection of the kidney is made and, with the exception of a small, well circumscribed, yellow, necrotic nodule within the cortex of the upper pole, no significant gross lesions are noted The calyces and the pelvis are slightly dilated

"Sections of the ureteral tumor reveal an irregular papillomatous structure which is covered by a thin layer of transitional epithelium The stroma of the papillomatous structure consists of a loose fibrous tissue which is moderately edematous in many areas and slightly to moderately vascular There are numerous irregular, dilated spaces throughout, which are empty Sections of the ureter reveal slight transitional epithelial hyperplasia with marked smooth muscle hypertrophy of the wall Sections of the kidney reveal a well circumscribed,

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ERAL INVOLVEMENT BY AORTIC ANEURYSM

J FREEMAN CRANE

ment of Urology, University of Southern California School of Medicine, Los Angeles, California

truction by abdominal aortic aneurysmal disease is not common, ct that the ureters are in close proximity to the aorta, however, ive uropathy should be fully appreciated, since the incidence of rtic aneurysm is increasing as the longevity of the population is ith an associated increase in the severity of degenerative vascular thermore, now that aortic aneurysms can be treated by surgical is all the more important to realize that ureteral involvement may cation in aortic surgery

ority of aneurysms of the abdominal aorta are of arteriosclerotic are a manifestation of segmental arteriosclerosis, even though the generalized Most of them arise below the origin of the renal arteries, m in character, and extend distally to involve the bifurcation Since lies to the left of the vertebral column, early growth of the aneurysm nfined to this side by aortic dilation and lengthening, however, as the increases in size, the bulk of the sac may be found on the right side ent of the common iliac arteries in conjunction with an abdominal urysm can also occur With weakening of the intima of the aorta there ng of the vascular coats and occasionally perforation of other tous plaques and finally the entire vascular wall may rupture, with hemorrhage into surrounding tissues This causes compression and nent of adjacent organs and vessels with resultant disruption of their physiological behavior

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URETERAL INVOLVEMENT BY AORTIC ANEURYSM

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Ureteral obstruction by abdominal aortic aneurysmal disease is not common, despite the fact that the ureters are in close proximity to the aorta, however, this obstructive uropathy should be fully appreciated, since the incidence of abdominal aortic aneurysm is increasing as the longevity of the population is extended, with an associated increase in the severity of degenerative vascular disease Furthermore, now that aortic aneurysms can be treated by surgical excision, it is all the more important to realize that ureteral involvement may be a complication in aortic surgery

The majority of aneurysms of the abdominal aorta are of arteriosclerotic origin and are a manifestation of segmental arteriosclerosis, even though the disease is generalized Most of them arise below the origin of the renal arteries, are fusiform in character, and extend distally to involve the bifurcation Since the aorta lies to the left of the vertebral column, early growth of the aneurysm will be confined to this side by aortic dilation and lengthening, however, as the aneurysm increases in size, the bulk of the sac may be found on the right side Involvement of the common iliac arteries in conjunction with an abdominal aortic aneurysm can also occur With weakening of the intima of the aorta there is splitting of the vascular coats and occasionally perforation of other atheromatous plaques and finally the entire vascular wall may rupture, with secondary hemorrhage into surrounding tissues This causes compression and displacement of adjacent organs and vessels with resultant disruption of their normal physiological behavior

The occurrence of ureteral obstruction by an aortic aneurysm has been previously reported De Weerd and associates demonstrated bilateral hydronephrosis with dilation of the upper third of each ureter in a patient with oliguria, uremia, and a large, pulsating abdominal mass Bilateral nephrostomies were done and subsequent abdominal exploration showed a large aortic aneurysm into the wall of which both ureters were incorporated

In Shumacker's case anuria developed while the patient was awaiting admission for operative excision of an abdominal aortic aneurysm Bilateral hydronephrosis and obstruction of the proximal ureters were demonstrated On surgical removal of the aneurysm both ureters were found to have been encased in the dense, fibrous, aneurysmal wall, with resulting ureteral obstruction The ureters were freed and subsequent pyelograms showed the obstruction to have been relieved

Occasionally an intact or dissecting aortic aneurysm will partially or completely occlude the renal arteries as they course across the aneurysmal sac, resulting in uremia, as reported in the cases of James, Halprin, and Bebner

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showed a large aneurysmal dilation of the aorta just below the left renal artery (fig. 1, *A*). The dilation extended down to the lower border of the third lumbar segment, where the aorta became quite markedly narrowed.

On March 23, 1955, exploratory laparotomy was done by the vascular surgeons. A large abdominal aortic aneurysm was found, with evidence of much periarterial inflammation. The aneurysm extended from a level above the renal arteries down to and including the bifurcation of the aorta and both common iliac arteries for a distance of 10 cm. The aneurysmal dilation of the left common iliac artery formed a dumbbell shape with the aneurysm of the aorta. In the depth of this dumbbell configuration the left ureter was found densely adherent and compressed. It was decided not to attempt resection of the aneurysm, because of its extent, and urological consultation was obtained. The left ureter was freed from the depths of its trapped position between the aneurysms of the abdominal aorta and that of the left common iliac. The ureter was transplanted to a position anterior to the aneurysmal dilation. At completion of surgery cystoscopy was done and the left ureter was easily catheterized to 30 cm. and drained clear urine. The catheter was left indwelling.

Following surgery, ileus developed and the output of urine diminished to between 500 and 750 cc. daily, for 5 days. The ileus subsided with gastrointestinal intubation and with this improvement the daily urinary output increased to 1,900 cc. by the sixth postoperative day. The left ureteral catheter was removed on the twelfth postoperative day, after making a withdrawal pyelogram, which showed some hydronephrosis and delay in drainage from the left kidney (fig. 1, *B*). The patient was discharged on the fourteenth postoperative day. At this time the blood urea nitrogen was 17 mg. per 100 cc.

The patient continued to have left lumbar pain. On May 21, 1955, he was readmitted to the hospital, when the pain in the back suddenly became most severe, and he had suffered marked weakness and collapsed. On examination the pulse was weak at 120 per minute. The blood pressure was only palpable at 110 systolic and the extremities were cool. He was alert and co-operative, but apprehensive. The abdominal examination was pertinent: in the left lateral half of the midabdomen a tubular, pulsating mass was palpated. A tubular mass was also present over the left iliac crest. The abdomen was full, distended, and dull to percussion. The hemoglobin was 9.8 gm. per 100 cc., red blood count 3,570,000, and the hematocrit 33 per cent cells. Urinalysis was normal except for albuminuria and numerous hyaline and granular casts.

It was felt that the patient now had a spontaneous rupture of the aortic abdominal aneurysm. Continuous transfusions of whole blood were given and he temporarily improved, but 18 hours after admission he expired. An autopsy was not obtained.

Case 2. D. R., a 53-year old white male supervisor, was seen March 19, 1956 with the following pertinent history.

In October 1955, aching pains gradually developed in the lumbar region. These pains became worse and radiated into the abdomen anteriorly and the inguinal regions. His doctor obtained an intravenous pyelogram that showed no ap-

Abdominal aortic aneurysm is not the sole vascular lesion capable of causing an obstructive uropathy A large arteriosclerotic aneurysm of the hypogastric artery was reported by Goodwin and Shumacker to have caused ureteral and bladder neck obstruction

In addition to ureteral obstruction, it has been pointed out by Uhle and also by Rusche and Bacon that aortic aneurysms may simulate symptoms of primary urologic disease by hemorrhage into the perirenal areas from rupture of the sac, by displacement of the kidney and ureter by this hemorrhage, or the unruptured sac itself, and by a combination of vertebral erosion and nerve root pressure in the lumbar areas

In the following two cases, one or both ureters were involved by an abdominal aortic aneurysm

CASE REPORTS

Case 1 C M , a 60-year-old salesman, was admitted to the hospital in March 1955, complaining of aching pains in lumbar region, mostly on the left side, for 10 months The pain was of aching nature and radiated around toward the groin, relieved by lying down and aggravated while standing There was a 25-year past history of thromboangiitis obliterans, which required amputation of the left lower extremity at midthigh in 1930

Physical examination showed blood pressure 120/80 and pulse 84 The heart was not enlarged, had a regular sinus rhythm, and no murmurs The lungs were normal The abdomen was soft, without tenderness or palpable masses Extremities showed nonpalpable radial arteries and an absence of the left leg

Laboratory findings showed a normal urinalysis, except for a trace of albumin and a few hyaline casts The blood count was normal Blood urea nitrogen was 17 mg per 100 cc and blood chlorides 100 m/Eq per liter Potassium 4 0 m/Eq per liter

An aortogram, made on March 8, 1955 to study the occlusive vascular disease,

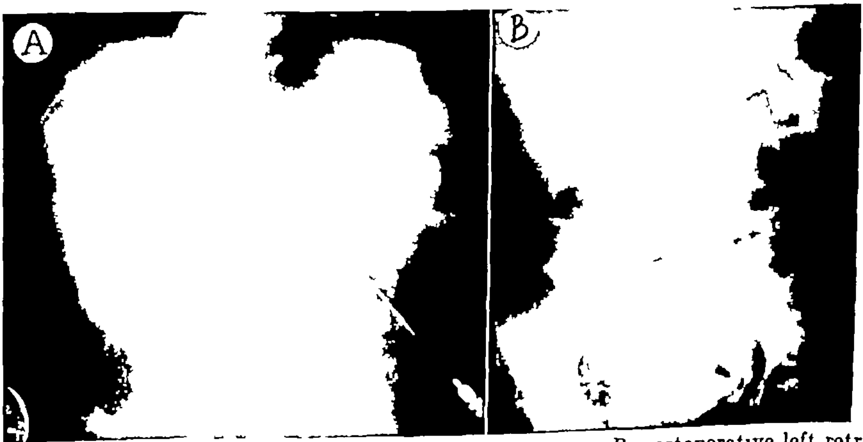


Fig 1 Case 1 *A*, aortogram, abdominal aortic aneurysm *B*, postoperative left retrograde pyelogram shows hydronephrosis and lateral displacement of ureter

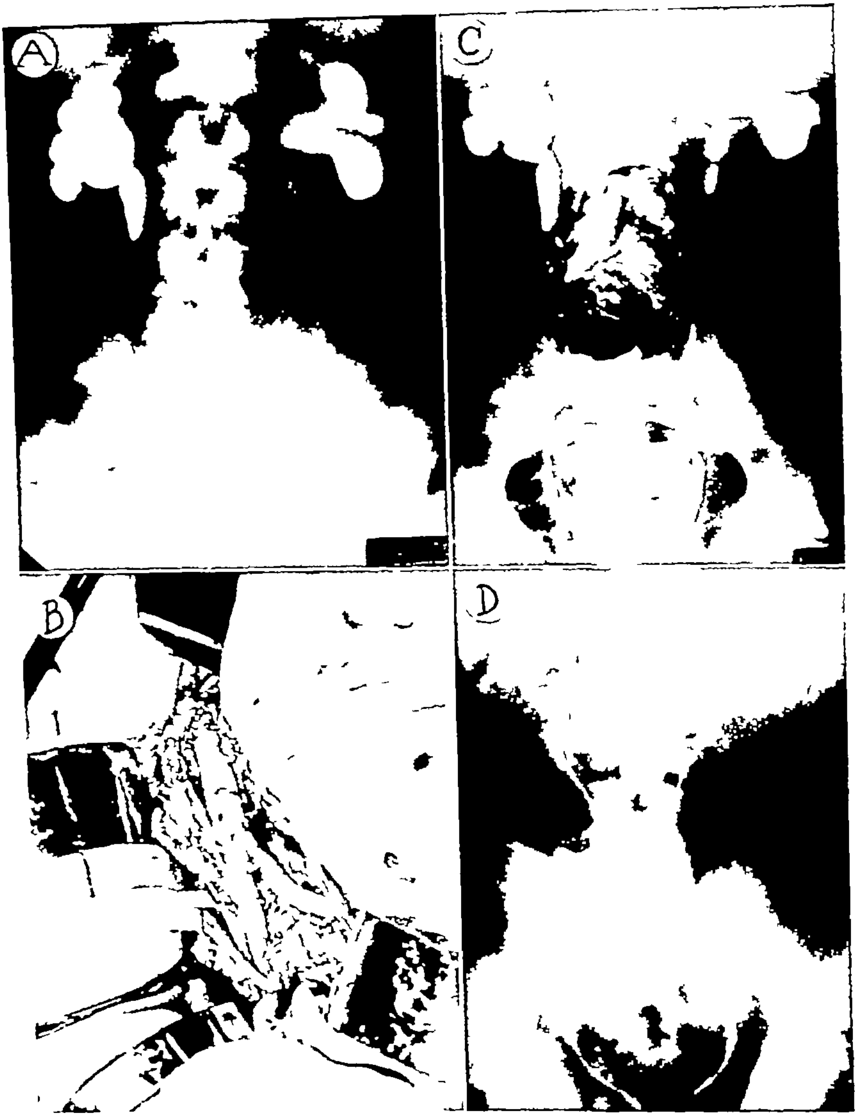


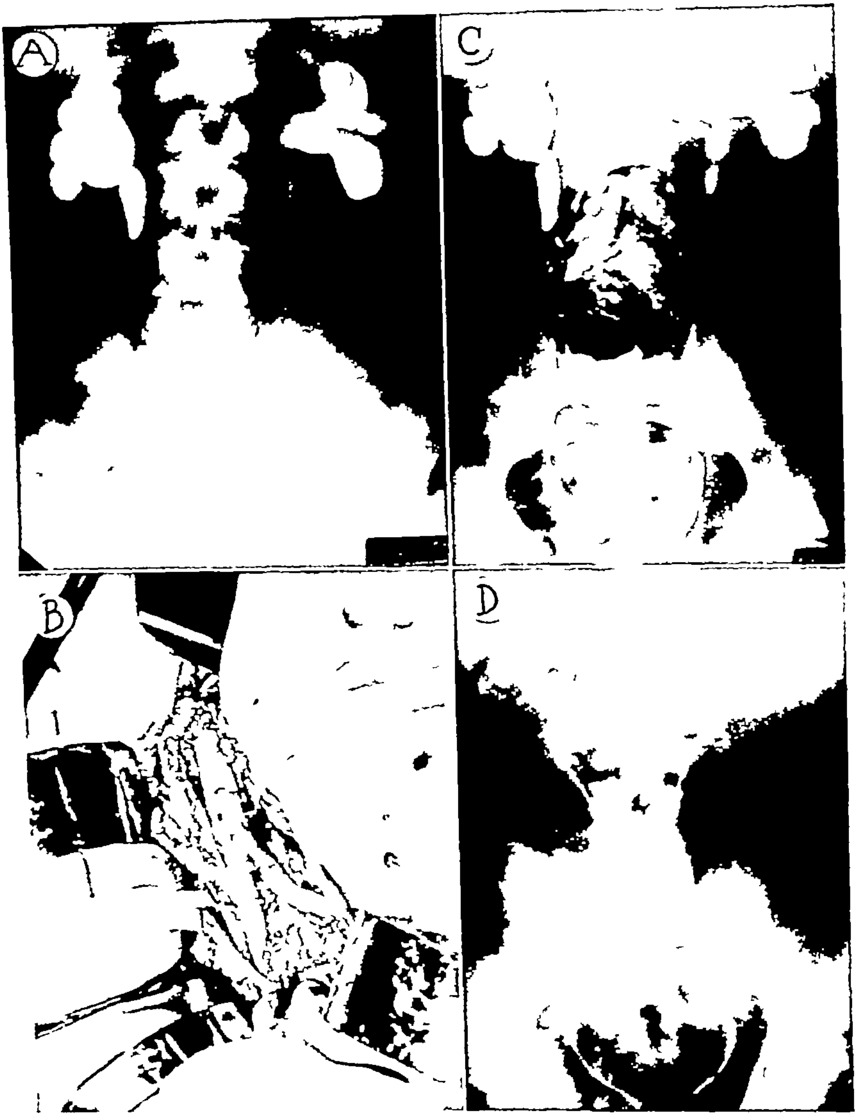
FIG 2 Case 2 A preoperative retrograde pyelograms show bilateral hydronephrosis, obstruction of segment of each ureter by aortic aneurysm B relation of freed ureters (tapes identify ureters) to completed aortic homograft C specimen of aortic aneurysm shown in relation to lumbar ureters on pyelogram D postoperative pyelogram Bilateral hydronephrosis has been relieved

connective tissue, was removed and the segment of aorta was replaced with an arterial homograft (fig 2, *B*) Examination of the specimen showed a prominent arteriosclerotic aneurysm measuring 9 cm in length, extending to the bifurcation of the common iliac arteries (fig 2, *C*) Encircling approximately one-half of the circumference of the aneurysm was a large mass of extensive collagen connective tissue 2 to 5 cm thick parent excretion of urographic medium by the right kidney, and a delay in excretion from the left kidney The delayed films disclosed a large hydronephrotic sac The patient was advised to have further urological investigation, but inas much as the pain subsided, he did not return Since that time he continued work ing, but had anorexia and a weight loss of 10 pounds Four months after the initial onset of symptoms, he was now seen because of recurrence of pain and, in addition, urgency of urination and some dysuria He gave no history of ve nereal disease and the blood Wassermann was negative

A summary of the physical findings showed the patient 5 feet 8 inches tall and he weighed 165 pounds The blood pressure was right arm, 140/80, left arm, 128/76, in supine position The heart and lungs were normal and the abdomen showed no tenderness or any palpable masses or organs The kidneys were neither palpable nor tender and the back was normal, without tenderness The external genitalia were normal and the prostate gland showed a benign enlargement

Urological investigation at the hospital showed a normal urinalysis, except for 8–12 white blood cells per high power field, and the urine cultures showed no growth The blood nonprotein nitrogen was elevated to 78 mg per 100 cc The blood Wassermann was negative Retrograde kidney study under anesthesia showed advanced bilateral hydronephrosis, due to bilateral ureteral obstruction at a point 5 cm distal to the ureteropelvic junction (fig 2, *A*) The area of obstruction in the ureters was symmetrical, 6 cm long, not displaced or distorted The distal third of the ureters was normal In the erect position there was no drainage from the kidneys and proximal 5 cm of both ureters Not until a catheter had been passed to the left kidney did indigo carmine appear from that side and none ever appeared from the right With anesthesia a large, firm, slightly movable, midline, faintly pulsatile mass could now be palpated in the epigastrium Gastrointestinal, colon, and chest radiological examinations were normal Electrocardiographic studies were normal Vascular studies indicated abdominal aneurysm and no obstruction to the vascular system The peripheral vessels were unobstructed

A diagnosis was made of probable aortic abdominal aneurysm with involvement and obstruction of the lumbar portion of the ureters Ureteral catheters were introduced to each kidney for drainage three days prior to abdominal surgery in conjunction with the vascular surgeons At operation a large mass was found surrounding both ureters and the aorta, extending from the renal artery level to the distal common iliac arteries The mass was resilient and palpably suggested synthetic rubber It was chronic inflammatory in appearance and surrounded the aorta for a distance of 2 inches The biopsy showed chronic inflammation and fibrosis The ureters were identified at the level of the common iliac arteries and traced upward The right ureter was freed from deep within the encircling mass of layered sheets of fibrotic tissue It was then incised longitudinally through its thickened fibrotic wall down to mucosa, to relieve the constricting fibrosis of its wall The left ureter was freed more easily from its more superficial position within the mass and likewise incised longitudinally The abdominal aortic aneurysm, together with its solid surrounding fibrous



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Ureteral catheters were left indwelling for 13 days, until a time when most urine came through the urethral catheter The average urinary output for the first 48 hours was 30 cc, the patient requiring hypotensive drugs to maintain the blood pressure and the nonprotein nitrogen rose to 145 mg per 100 cc On the second postoperative day urinary output increased to 825 cc and then was copious, averaging 2,925 cc per day from the left kidney, but up until the time the ureteral catheters were removed, the right kidney excreted but 19 cc average per day, with no excretion of phenolsulfonphthalein The nonprotein nitrogen declined and by the fourteenth postoperative day it was 34 mg per 100 cc On the fifteenth postoperative day he was dismissed from the hospital

The convalescence continued good The nonprotein nitrogen was 34 mg per 100 cc six weeks postoperatively He had moderate pyuria with B proteus and E coli growth on culture, but was asymptomatic and returned to his usual work and activities Three months after the surgery an intravenous pyelogram was made, the nonprotein nitrogen being 37 5 mg per 100 cc This showed that the left kidney and ureter were normal in function and appearance, but the right kidney was still showed poorly visualized, due to impaired excretion of the medium On July 20, 1956, retrograde pyelograms were done Indigo carmine failed to appear from the right ureteral orifice during this study, excretion from the left orifice was satisfactory The ureters were easily catheterized Pyelograms showed that the bilateral hydronephrosis had been relieved and that the ureters were unobstructed (fig 2, *D*) Recovery seemed good and the patient has continued asymptomatic 11 months postoperatively

SUMMARY AND CONCLUSIONS

Two cases of ureteral obstruction by abdominal aortic aneurysms are presented In one case, at abdominal exploration, the left ureter was found to be displaced by the aortic aneurysm, which extended into the common iliac artery In addition to being adherent to the aneurysm wall, the ureter was caught and compressed by the two opposing aneurysms of the common iliac and aorta Although the aortic aneurysm could not be removed, the ureter was freed and replaced from its entrapped location, to permit better drainage This did not afford as good a result as anticipated

In the second case bilateral hydronephrosis resulted from nearly complete obstruction of a large segment of the upper ureters by an aortic aneurysm Extensive collagenous connective tissue forming the aneurysm wall had encased both ureters, obstructing them Following preoperative ureteral drainage, the ureters were freed at the time of excision of the abdominal aortic aneurysm and arterial homograft Surgery resulted in relief of the azotemia and ureteral obstruction, as shown by postoperative studies

In cases of hydronephrosis of extrarenal origin, ureteral obstruction by aneurysms of the abdominal aorta should be considered The ureters, when involved, may be adherent, or even encased within the wall of the aneurysm This possibility should be regarded when one is confronted in surgery with cases of nonsuppurative retroperitoneal inflammatory masses involving the ureters, lest the mass be the wall of an aneurysm

Since ureteral involvement may be a complication of surgery on large abdominal aortic aneurysms, preoperative excretory urograms would seem advisable

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PERIURETERITIS OBLITERANS A RETROPERITONEAL INFLAMMATORY DISEASE

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In recent years reports of an unusual disease affecting the retroperitoneal tissues surrounding the ureter have appeared in the literature The lesion described has caused hydronephrosis by producing segmental compression and obliteration of the ureter It has been called periureteritis plastica, periureteral fibrosis, retroperitoneal inflammation of the ureters and nonspecific hydronephrosis Similarities in both the descriptions and in the pyeloureterograms in these case reports indicate a common entity The purpose of this paper is to unify the concept of the disease, report additional cases, describe the means of diagnosis, indicate the choice of treatment and to theorize an etiology

The term, periureteritis obliterans is suggested as best describing the condition as it is met with clinically

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pyelonephritis requiring nephrectomy Cultures of the tissues around the ureters and ureteral biopsy were made in each instance Pyeloureterograms one and two years later showed no hydronephrosis The hypertension has not persisted Cultures of the tissue produced growth of B aerogenes and hemolytic Staph albus, sensitive to chloromycetin Cultures of the prostatic secretion showed the same organisms (fig 1)

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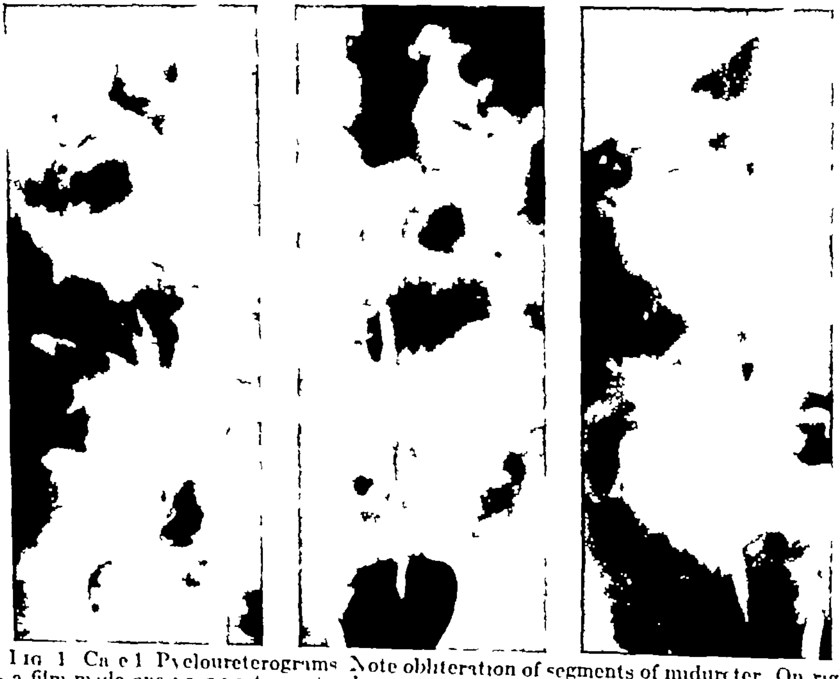

Fig 1 Case 1 Pyeloureterograms Note obliteration of segments of midureter On right is a film made one year postoperatively

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PERIURETERITIS OBLITERANS A RETROPERITONEAL INFLAMMATORY DISEASE

WILLIAM P MULVANEY

From the Department of Urology, Good Samaritan Hospital, Cincinnati, and the Division of Urology, College of Medicine, University of Cincinnati, Ohio

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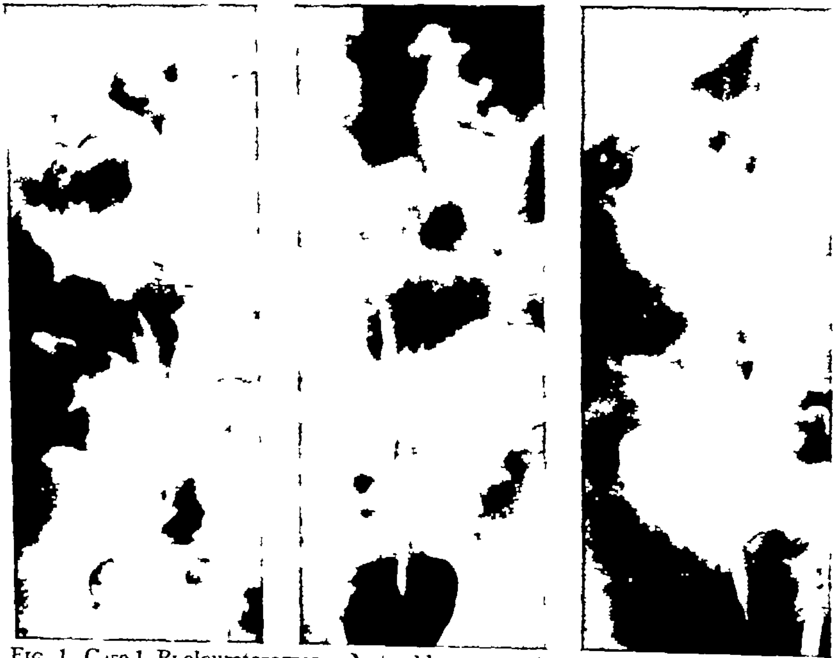

FIG. 1. Case 1. Pyeloureterograms. Note obliteration of segments of midureter. On right is a film made one year postoperatively.

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August 1955 revealed hydronephrosis with obstruction of the ureter at the pelvic brim (fig 3) No other significant findings existed Exploration showed the typical fibrous tissue compression of the ureter in the midportion This was easily excised from the ureter by sharp dissection A 2 cm segment appeared to be almost obliterated Segmental resection and anastomosis were made followed by recovery She has remained asymptomatic Urine and periureteral cultures produced a growth of B aerogenes

OPERATIVE FINDINGS AND PATHOLOGY

The midureter in each case was enveloped by a dense, matted, fibrous tissue mass (fig 4) It extended laterally over the posterior abdominal muscles and medially across the psoas muscle Anteriorly the peritoneum was adherent but could be dissected bluntly without much difficulty The fibrous tissue was extremely dense and surrounded the ureter intimately The fibrous mass reportedly has been large enough to palpate through the abdomen in some cases It has been confused with neoplasm until biopsy has been made A cleavage plane could be developed by following uninvolved ureter into the scarred area By blunt and sharp dissection the crisp rigid tissue could be peeled from the strangulated ureter leaving the underlying ureteral wall pale, indurated and edematous The lumen of the ureter was reduced in each case and almost obliterated in two

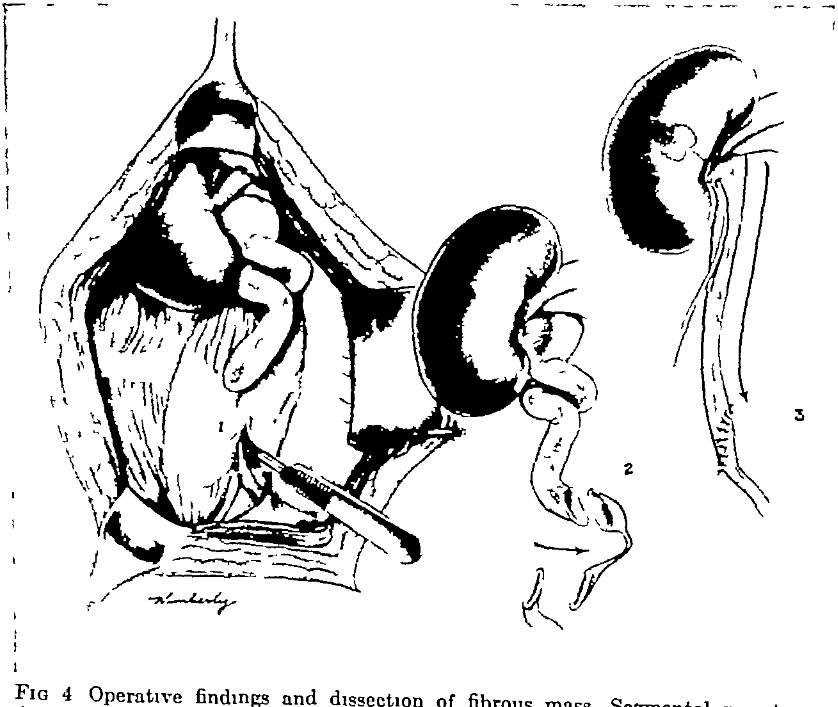

FIG 4 Operative findings and dissection of fibrous mass Segmental resection and ureteroureterostomy

Urinary output from the right kidney was good but the uremia progressed With the patient in critical condition a left nephrostomy was made on November 22 with the hope of reversing the downward course The patient died of uremia on November 29

Case 3 A 26-year-old woman had been treated for six attacks of pyelonephritis in the right kidney over a five-year period Retrograde pyeloureterography in

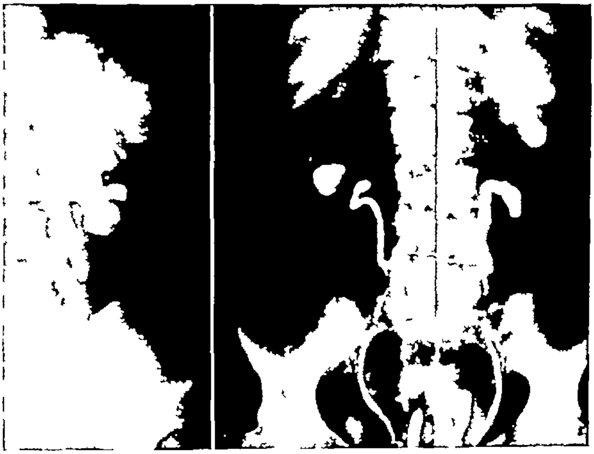

FIG 2 Case 2 Demonstration of typical ureterograms with segmental obliteration and hydronephrosis

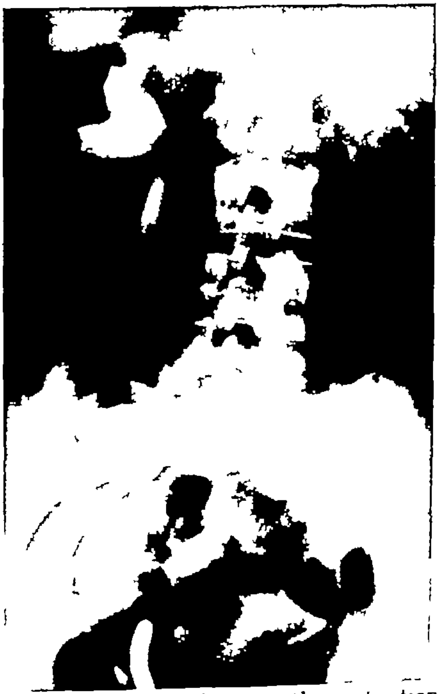

FIG 3 Case 3 Unilateral hydronephrosis with constriction at pelvic brim

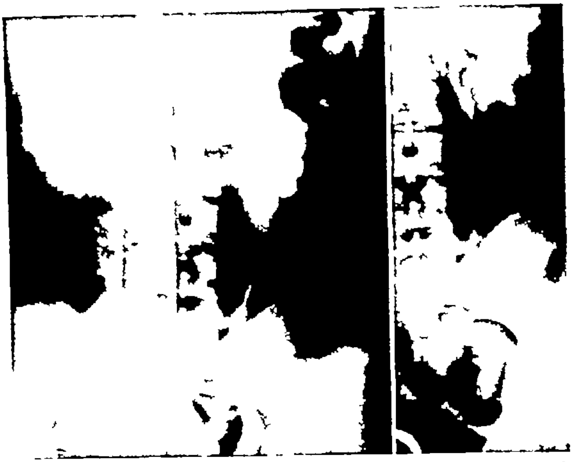

FIG 5 A case simulating but probably not representing periureteritis obliterans Nonfunction on right Short constriction and fibrosis treated by Foley-Y-plasty, postoperative result one year later

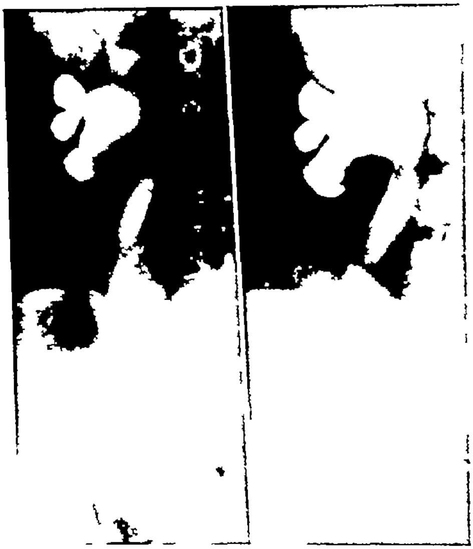

FIG 6 Inadequate filling of ureter (left) simulates periureteritis. Complete filling (right) shows uniform dilatation

Inadequate filling of the ureter in cases of hydroureter can simulate the disease (fig 6) Obviously a good ureterogram is necessary

Final diagnosis depends upon the operative findings of periureteral fibrotic masses encompassing and strangulating the ureter (fig 7)

TREATMENT

A review of the cases reported leads one to some general conclusions The first is that surgery should not be delayed Response does not seem to be as good as in

Resection of these portions allowed use of ureter of adequate caliber for anastomosis

Biopsies of the ureteral wall and of surrounding fibrous tissue showed nearly identical findings "Dense, wavy, collagenous connective tissue was separated by pronounced interstitial edema The interstices were infiltrated by lymphocytes and a few neutrophils There were focal aggregations of lymphocytes The inflammatory reaction is of nonspecific character "* The pathogenesis of the disease would seem to be nonspecific response to infection There is no common denominator in the cases reported thus far nor any explanation for the localization of reaction in the midureters It may be of significance to note that constriction of the ureters seems to occur at the pelvic brim in females and somewhat higher in the male patients The association in our cases and others with bacteria commonly infecting the urinary tract may indicate an ascending infection There is a lack of coincidental disease in other organs to implicate a source Vest cited the demonstration by Parker that the lymph channels of the ureter are placed longitudinally in the adventitia and distributed into the abdominal, common iliac, and hypogastric lymph nodes He mentions pertinently that Kenneth Walker traced the migration of dye from the urethra to the upper ureter by way of the surrounding plexus of lymphatics Pigment injected into the base of the bladder was seen in the tissue around the ureter 48 hours later The periureteral tissue contained inflammatory cells bearing particles of dye while the ureteral wall did not, demonstrating that lymphatic pathways do exist to explain the peculiar localization of the fibrosis Particles of dye placed in the uterine cervix show a similar collection in the lymphatics

The bacteria isolated are known to produce a nonspecific inflammatory reaction as seen in these cases and are encountered commonly in urinary tract disease Periureteritis obliterans therefore most likely originates from a lower genitourinary tract infection

DIAGNOSIS

The appearance of the lesion when visualized by retrograde pyeloureterography can be said to be typical The use of a bulb type ureteral catheter gives by far the best demonstration of the disease A good ureterogram is essential to assess the involvement accurately and to plan the surgical treatment Since it may be impossible to pass an ordinary ureteral catheter through the narrowed segment, the use of a bulb catheter may make a difficult diagnosis certain Neomycin added to skiodan is suggested to lessen the hazard of pyelography in these cases

The finding of hydronephrosis with hydroureter in the upper third with segmental constriction of the midureter should suggest the diagnosis of periureteritis obliterans This may be unilateral or bilateral If unilateral, involvement of the opposite side must be anticipated Iozzi and Murphy treated a unilateral case and found the same process developing in the other kidney four months later

An extremely short area of constriction is easily confused with stricture (fig 5)

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* Pathology report of W T Collins, M D

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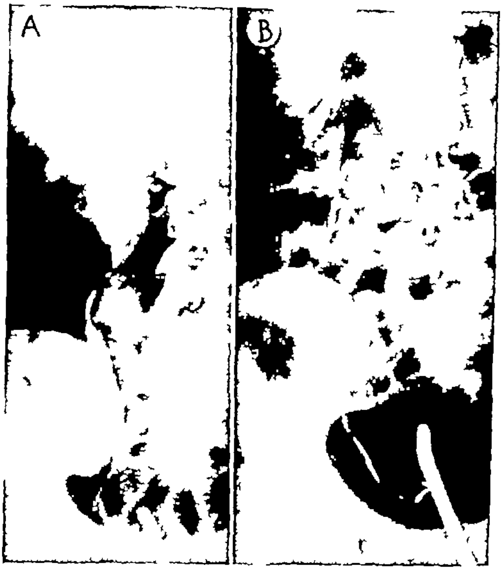

Fig 7 *A*, periureteritis without gross fibrotic mass treated by lysis Obliteration by fusiform fibrosis which may or may not represent typical periureteritis obliterans *B*, recurrent right pyelonephritis demonstrates deformity suggesting periureteritis obliterans Exploration not done to date

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The density of fibrous reaction about the ureter causes serious concern in regard to possible recurrence of obstruction if lysis alone is used The ureters are obviously damaged and if almost obliterated, segmental resection seems to offer the best hope for cure However, lysis has given good results and no long term failures have been reported to our knowledge Time and experience will decide the preferred treatment

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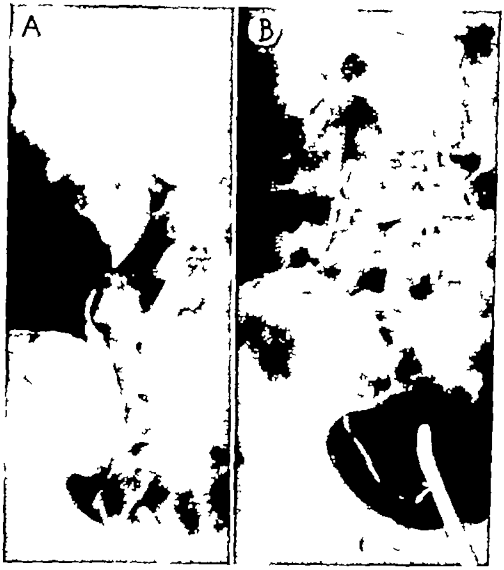

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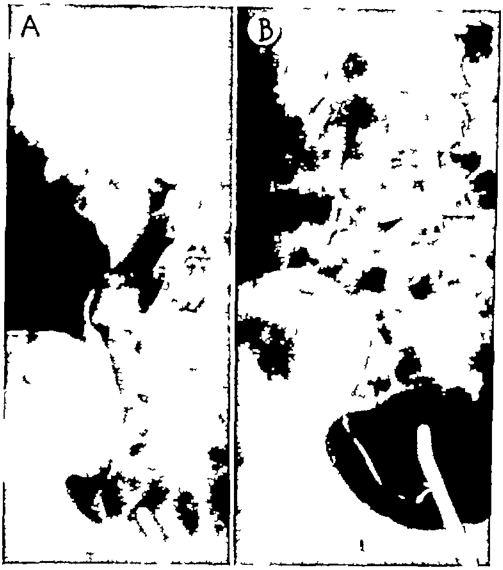

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TABLE 1 *Tumors of ureter*

Benign				Malignant			
	Sex	Age	Side		Sex	Age	Side
W M	M	39	L	I.M	F	68	R
R A	M	19	L	H.R	M	57	L
R B	F	45	R	E.M	F	69	L
				H S	M	63	L
				E H	F	71	R
				M E	F	64	R

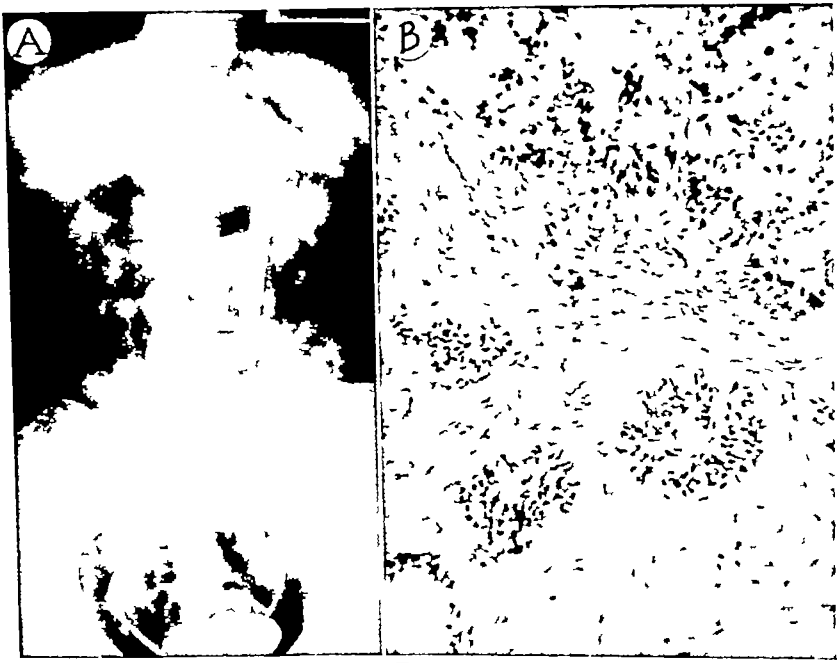

FIG 1

deformity in the lower portion of the right ureter (fig 1, A) On July 28 a subtotal right nephro-ureterectomy was accomplished

A definition of terms should be included' "Subtotal nephro-ureterectomy This term is used for operations that did not include removal of the intramural segment of the ureter" 'Complete nephro-ureterectomy This group includes excision of the ureteral orifice with variable amounts of the contiguous vesical wall" This is Culp's definition

The pathologic diagnosis was 'right hydronephrosis and a papillary tumor 15 cm from the right kidney and located in the right ureter" On microscopic examination the tumor was seen to be a papillary growth consisting of finer and coarser epithelial cells and occasional instances showing squamous metaplasia and mitotic figures which were not frequent An occasional prolongation of cells

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PRIMARY TUMORS OF THE URETER CASE REPORTS

L G WOOD and G E HOWE

Primary tumor of the ureter has always been considered a very rare disease but recent reports in the literature suggest that it should be changed from the rare to the infrequent class The total number of primary malignant ureteral tumors as of July 1, 1954 is listed at 454 cases, whereas 138 benign ureteral tumors have been reported in the literature Unquestionably, many more cases of primary ureteral tumors have been encountered but not reported for various reasons We have had a private series of nine primary ureteral tumors since 1948 Four of these patients were seen during the past 18 months

It is not the purpose of this paper to present an exhaustive review of the literature of the multiple ramification of conflicting views in terminology when one ponders the problem of etiology Excellent reviews by Abeshouse,[1] Whitlock,[2] Culp[3] and MacLean[4] cover this subject thoroughly Instead we wish to present a critical analysis of nine cases of primary tumors of the ureter, including a review of symptomatology, diagnostic techniques, treatment, pathology and periodic followup

Table 1 is a representative summary of the cases and in general agrees with the literature as to age, side, and sex It should be pointed out that solitary papilloma has been classified as benign in spite of the fact that it is potentially a malignant tumor by virtue of its tendency to develop into papillary carcinoma in untreated patients or to recur in a malignant form in treated patients The results of operative treatment of malignant ureteral tumors, as reported in the literature, have been disappointing from the standpoint of curability and longevity In our series, one death was due to carcinoma of the ureter, in none of the others has a recurrence been demonstrated

CASE REPORTS

Case 1 I M (Hosp No 56-6937) A 68-year-old white woman was seen in Royal Columbian Hospital on July 20, 1948, with a four-month history of right flank pain and hematuria Repeated urinalyses showed gross and microscopic red blood cells An intravenous pyelogram showed a nonfunctioning right kidney On cystoscopic examination the operator was unable to pass a ureteral catheter more than 10 cm up the right ureter, after which blood came from the right ureteral orifice Retrograde pyelograms demonstrated a typical goblet-shaped

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Read at annual meeting of Western Section of American Urological Association Seattle Wash , May 27–30, 1957

[1] Abeshouse, B S Primary benign and malignant tumors of ureter Am J Surg , 91 234 1956

[2] Whitlock, G F , McDonald, J R and Cook, F N Primary carcinoma of ureter Pathologic and prognostic study J Urol , 73 245 1955

[3] Culp, O S Treatment of tumors of the renal pelvis and ureter Trans Am Assoc Genito urin Surg , 47 101, 1955

[4] MacLean, J T Pathology of tumors of the renal pelvis and ureter J Urol 76 384, 1956

The tumor was destroyed by electrocoagulation On November 16, another cystoscopy revealed a small recurrence measuring less than one-half centimeter in diameter just lateral to the left ureteral orifice This was again destroyed by electrocoagulation

It was noted that a small papillary growth protruded from the left ureteral orifice whenever ureteral peristalsis took place On November 21 cystoscopic examination and retrograde pyelography were repeated Again, a small papillary projection was seen protruding from the left ureteral orifice However, the left kidney and the remainder of the ureter appeared normal Further operative procedures were declined by the patient because of severe anginal attacks On March 28, 1951, another cystoscopic examination failed to reveal any evidence of tumor in the bladder However, the small papillary tumor was again noted protruding from the left ureteral orifice and therefore a fulgurating tip was inserted 1½ cm up the left ureteral orifice and the whole area thoroughly fulgurated Following this left ureteral meatotomy was performed with the Kearns knife Another checkup was made October 30 No recurrence was noted Retrograde pyelograms and ureterograms showed no abnormality Anterior myocardial infarction developed January 28, 1952, and he died three days after admission to

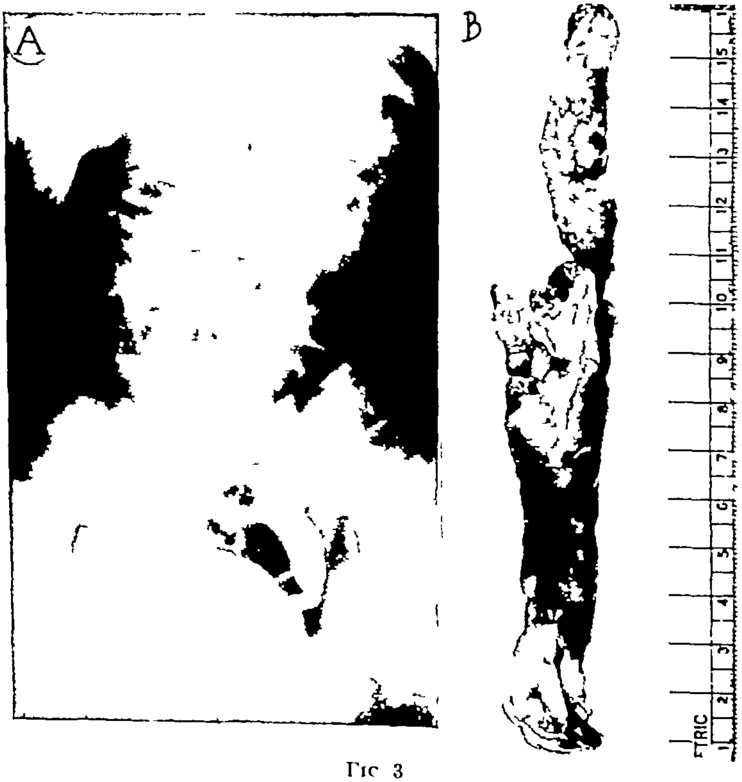

FIG 3

was located in the more superficial portion of the muscularis but generally speaking infiltration was slight This would appear to be a grade 2 malignancy (fig 1, *B*)

The patient has continued to enjoy a full and useful life for the past eight and one half years and at the present time is free of any urinary symptoms and/or tumors of her genitourinary tract

Case 2 M E (Hosp No 11829, V G Hospital) A 64-year-old white woman was admitted to the Vancouver General Hospital on February 26, 1950, with a three-month history of painless hematuria On February 28, cystoscopic examination and retrograde pyelography demonstrated a goblet-shaped filling deformity in the lower end of the right ureter, much the same as in figure 1, *A* On March 2, a subtotal nephro-ureterectomy was performed

The pathologic diagnosis was hydronephrosis and a tumor of the lower third of the right ureter Microscopic examination revealed a well differentiated transitional cell carcinoma with cells regular in type but mitoses present indicating active growth Slight superficial infiltration of the submucosal layer was present and no tumor was seen in the muscular layers or the attached serosal tissue (fig 2, and note "squamous metaplasia") In addition it was noted that 4 cm normal distal ureter was present For the past seven years the patient has been free of symptoms referable to her urinary tract and has had no recurrence of tumor

Case 3 H S (Hosp No 1920) A 63-year-old white man was seen at a consultation in St Vincent's Hospital on June 14, 1950, with the complaint of painless hematuria which had occurred three times during the past five months In addition it was noted that prior to the past six months he had suffered a posterior myocardial infarct On June 17, cystoscopic examination revealed an area of carcinoma 1 cm in diameter that surrounded the left ureteral orifice

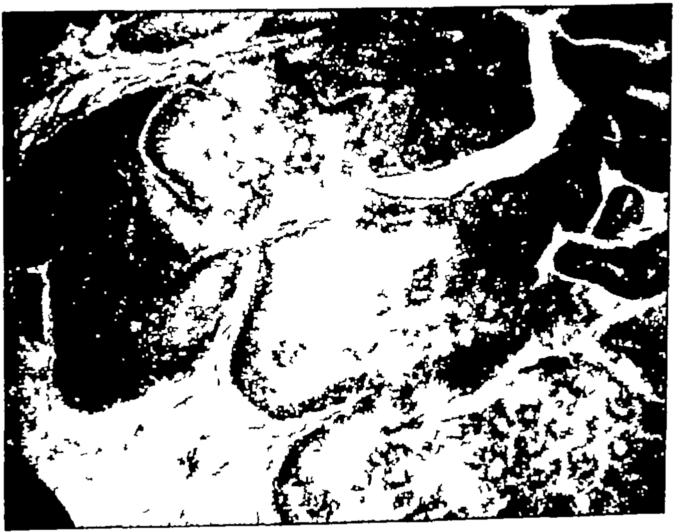

FIG 2

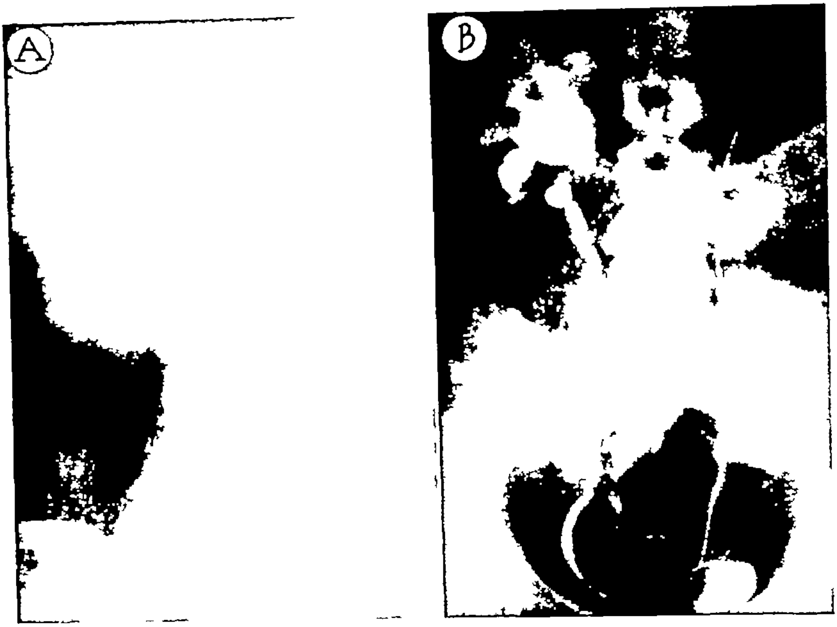

FIG 5

venous urograms performed elsewhere in the Province showed a nonfunctioning right kidney She volunteered the additional history that she had had one attack of painless hematuria four years earlier Physical examination was not remarkable except for mild right costovertebral angle tenderness Urinalysis showed 10 to 12 red blood cells per high powered field On November 14, at cystoscopy, right hydronephrosis was noted, due to an obstruction 2 cm below the ureteropelvic junction (fig 5) On November 18 a subtotal right nephro-ureterectomy was performed Microscopic examination of the upper portion of the right ureter revealed a nodule underlying the ureteral mucosa on one side and completely replacing the muscular and other layers of the wall in this part The nodule was composed of hyalin material (fig 6, *A*) On staining with Masson's trichrome method the section was found to contain a mixture of smooth muscle and fibrous connective tissue confirming the diagnosis of leiomyoma of the ureter (fig 6, *B*)

Comment This is a benign tumor and demonstrates that ureteral tumors can involve any of the layers of the ureteral wall The patient has been well and free of symptoms following operation

Case 6 H R (Hosp No S56-2705) A 57-year-old man was first admitted to Mount St Joseph's Hospital on February 19, 1956 He gave a history of gross, total, painless hematuria three weeks earlier Since the initial episode of hematuria, his urine had been port wine in color and had continued to be painless Physical examination was within normal limits except for many red blood cells in the urine On February 20 cystoscopic examination and retrograde pyelography revealed left hydronephrosis and a suggestion of several radiolucent areas

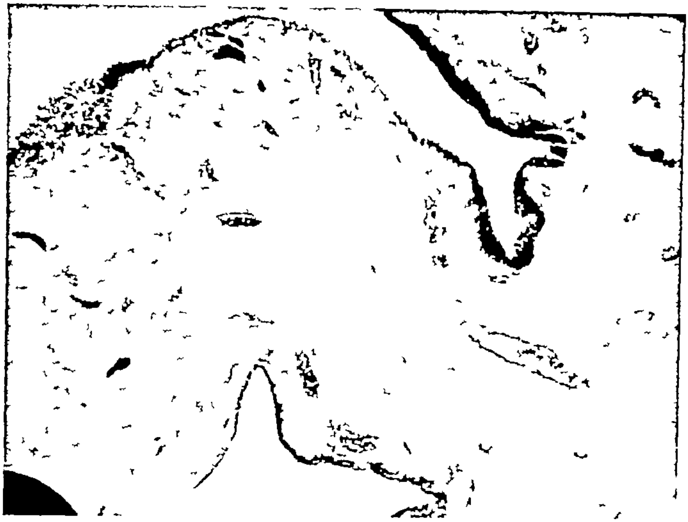

FIG 4

the hospital Autopsy disclosed no evidence of carcinoma in the genitourinary tract

Case 4 R.A (Hosp No 43352) A 19-year-old white man was admitted to the Vancouver General Hospital on February 25, 1951, complaining of painless hematuria of 10 days' duration He gave a history of having one other similar attack two years previously A previous cystoscopy on February 19 showed a filling defect in the lower half of the left ureter (fig 3, *A*) The right kidney was normal as were the bladder and urethra The operator was unable to pass the catheter beyond the 15 cm level Therefore, an intravenous urogram on February 21 showed normal kidneys and again a filling defect in the lower third of the left ureter On March 1, an exploration of the entire left ureter was performed and a gelatinous mass was felt inside the ureter The ureter was then opened from the ureteropelvic junction to the brim of the pelvis and a tumor noted, attached to the mucosa of the ureter at the ureteropelvic junction and extending down to just above the bladder The tumor was freed by sharp dissection and removed The ureter was then closed over a catheter and the kidney and ureter left intact The tumor was recognized as a polyp (fig 3, *B*), it measured 16 cm in length and 2 cm in width at its distal end On microscopic examination the central portion consisted of loose fibrous connective tissue with large dilated blood vessels and was covered by regular transitional cell epithelium with no evidence of malignancy (fig 4) This was a benign ureteral polyp resembling in many respects a nasal polyp The patient has been well the past six years with no evidence of any damage to his urinary tract on either side

Case 5 R B (Hosp No 143257) A 45-year-old white woman was admitted to Vancouver General Hospital on November 13, 1953, with a history of two attacks of right pyelonephritis over the preceding two years Four weeks before being seen she had symptoms of severe cystitis with right flank pain Two intra-

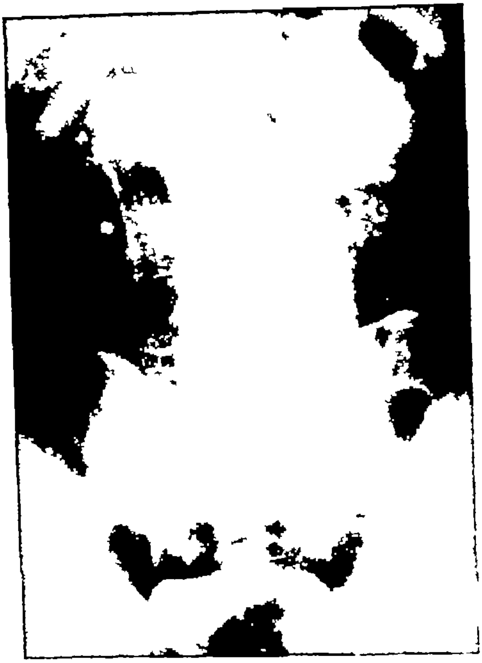

FIG 7

measuring 1½ cm at its base and located on the floor of the bladder between the ureteral orifices This was resected and the diagnosis was anaplastic transitional cell carcinoma of the bladder, invasive and grade two in nature

Comment This demonstrates the importance of followup cystoscopic examinations

Case 7 E.H (Hosp No 235321P) A 71-year-old white woman was first admitted to the Vancouver General Hospital on May 19, 1956, complaining of pain in the right costovertebral angle, and hematuria Her symptoms, intermittent in nature, dated back eight months Physical examination was normal except for a fullness in the right flank and right lower quadrant Urinalysis showed 20 to 30 red blood cells per high powered field On May 19, at cystoscopy, the bladder and left kidney were found to be normal However, attempts to pass a catheter up the right ureter and to use various bulb catheters to inject dye up the right ureteral orifice were unsuccessful Bimanual vaginal and rectal examination at the time of cystoscopy revealed a hard, fusiform mass running up along the course of the right ureter On May 22 complete right nephro-ureterectomy was performed The entire ureter was found to be filled with tumor tissue Microscopic examinations of sections from the distal end of the ureter revealed that the wall of the ureter was extensively infiltrated by proliferating masses of malignant transitional epithelial cells Clumps of tumor cells were present in the thin-walled vessels The kidney was hydronephrotic (fig 8) She was re-admitted to St Vincent's Hospital on July 7 with abdominal distention On July 17 an

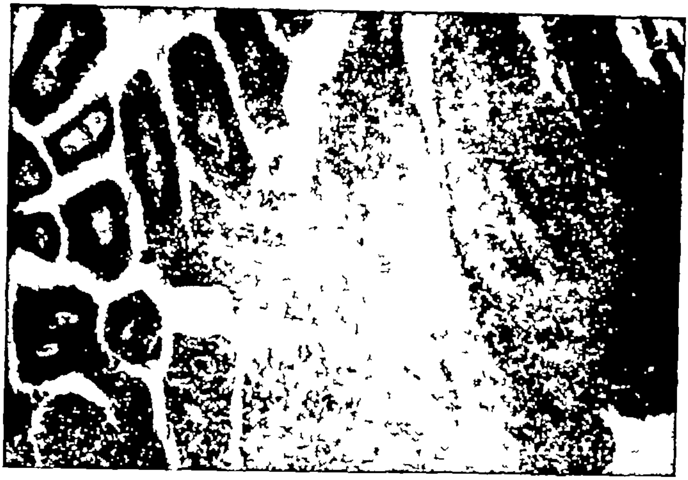

Fig 8

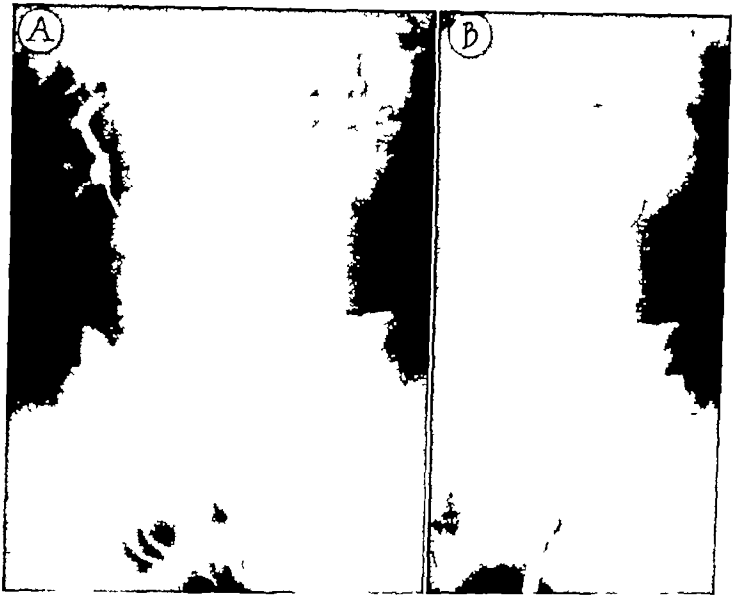

Fig 9

abdominal paracentesis showed cells consistent with adenocarcinoma on Papanicolaou stain On July 23, at the family's insistence, an abdominal laparotomy was done and revealed diffuse carcinomatosis Right retroperitoneal biopsy disclosed anaplastic transitional cell carcinoma, probably originating from the ureter The patient expired July 24

Comment Death occurred 11 months after the first symptoms of hematuria and right costovertebral angle pain, or 2½ months after the surgical procedure This is the only death in our series due to carcinoma

Case 8 W M (Hosp No 250389) A 39-year-old white man was first admitted

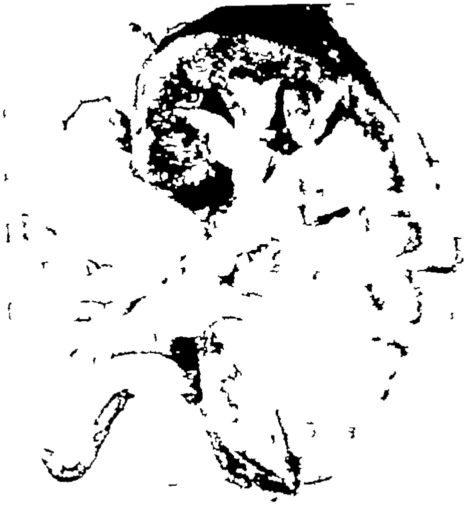

FIG 10

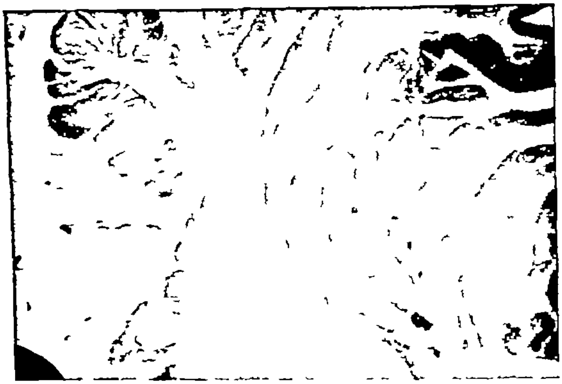

FIG 11

to Vancouver Hospital on August 26, 1956, complaining of painless hematuria He had had three attacks of hematuria since June 1956 Physical examination was not remarkable and urinalysis was also within normal limits On August 27, cystoscopy disclosed that the bladder was negative, left retrograde pyelography showed mild hydronephrosis and a peculiar, irregular point of obstruction at the pelviureteral junction (fig 9) A ureterogram, obtained with the use of the Braasch bulb, demonstrated a typical goblet-shaped filling deformity in the upper third of the left ureter, consistent with a papillary tumor of the ureter On August 30, a left subtotal nephro-ureterectomy was performed On opening the specimen it was noted that there was a fronded structure arising from the upper ureter (fig 10) Microscopic examination showed good differentiation of transitional cells and no evidence of submucosal infiltration (fig 11) The diagnosis was transitional cell papilloma of the ureter and mild hydronephrosis This was classified under benign tumors in our series, but knowing full well that it was potentially a malignant tumor, we asked the patient to return for further surgery He was readmitted to hospital and on December 11 the remainder of the left ureter and a portion of the contiguous vesical wall were removed Pathologic specimens showed no evidence of a pathological process in the ureter The patient has been free of symptoms for 10 months following surgery

Case 9 E F (Hosp No 79842) A 69-year-old white woman was admitted to Vancouver General Hospital on November 5, 1956, complaining of painless hematuria of six weeks' duration She also gave a history of frequency and symptoms of cystitis, which had been present in 1952 On April 24 of that year a cystoscopic examination with retrograde study revealed normal kidneys and no evidence of pathological processes in her bladder or urethra On October 23, just before her present admission, a cystoscopic examination again was negative However, the left ureteral catheter could not be passed beyond the 7 cm mark A left bulb ureterogram demonstrated a tumor in the lower third of the left ureter (fig 12) Physical examination under anesthesia revealed a small mass in the left lower quadrant measuring 2 cm in diameter and 4 cm in length On November 6, a subtotal left nephro-ureterectomy was performed Gross pathologic examination of the specimen showed left hydronephrosis and a tumor of the lower third of the left ureter (fig 13, *A*) Microscopic sections showed a well differentiated transitional cell carcinoma with occasional mitotic figures There was extensive infiltration of the wall of the ureter In one area there was a focus

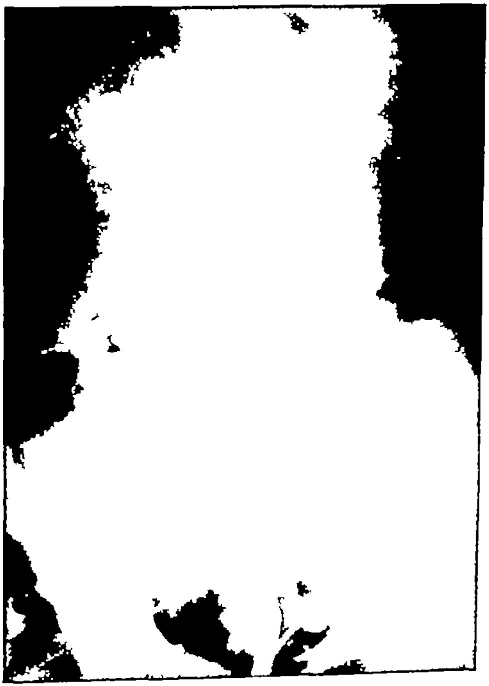

FIG 12

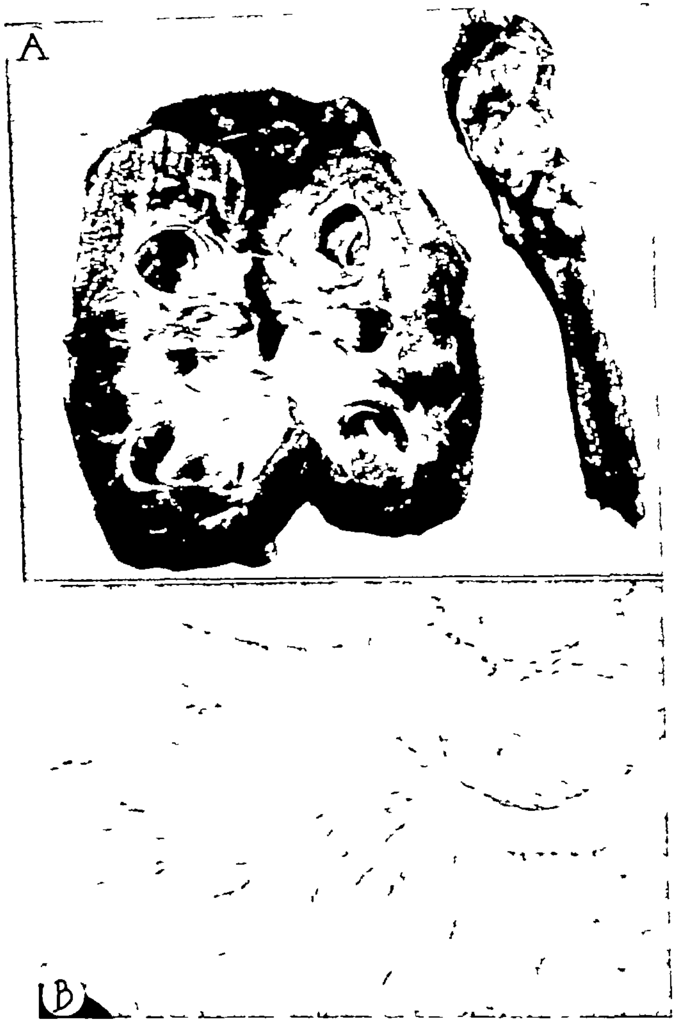

FIG 13

of transitional cell carcinoma more anaplastic and undifferentiated than the rest of the tumor (fig 13, *B*) For the past seven months following surgery the patient has been well and aside from slight frequency of urination, which responded well to vesical irrigations with clorpactin, she has had no symptoms referable to the urinary system No demonstrable evidence of recurrence has been noted

SUMMARY AND CONCLUSIONS

Nine cases of primary tumors of the ureter have been presented Two of these were definitely benign and one was classified as benign, although the pathologic diagnosis was benign papilloma of the ureter The authors realized that this was potentially a malignant tumor by virtue of its tendency to develop into a papillary carcinoma, and performed complete nephro-ureterectomy The remaining six were definitely cases of transitional cell carcinomas of the ureter and were treated as follows One by complete right nephro-ureterectomy, the only patient who expired 2½ months after the diagnosis was made, one by fulguration of the tumor in the ureteral orifice, the patient expired eight months later from myocardial infarction, no evidence of tumor was found at autopsy The remaining four were treated by subtotal nephro-ureterectomy and all are alive and well without demonstrable evidence of genitourinary disease at this time The period of elapsed time after operation in these latter four cases has varied from eight and one-half years to six months While we believe that the operation of choice for a malignant tumor of the ureter is a complete nephro-ureterectomy, i e , removal of the kidney, ureter and contiguous bladder wall, excellent results have been obtained in selected cases by a subtotal nephro-ureterectomy, i e , removal of the kidney and ureter to the bladder wall The poor results of operative treatment of malignant ureteral tumors, as reported in the literature, need not discourage the urologist Several principles can be laid down as a guide to early diagnosis

A diagnosis of ureteral tumor is best made by cystoscopy and a bulb pyelo ureterogram One should always do this procedure in any case of unexplained hematuria

Papillary carcinoma of the ureter in all our cases showed a goblet shaped filling defect

Whenever pain is due to a ureteral tumor, hydronephrosis is present Every case of hydronephrosis should be checked for the possibility of ureteral tumor

The authors can only reiterate by quoting the following passage from Abeshouse "One should remember that infiltrating ureteral neoplasms are frequently diagnosed as stricture of the ureter and stricture of the ureter with accompanying hydronephrosis is rare in patients of the carcinoma age group For all intents and purposes, stricture of the lower third of the ureter in this age group should be regarded as malignant until proven otherwise "

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TOPICAL ANESTHESIA OF THE VESICAL MUCOSA AS A TOOL FOR THE MANAGEMENT OF THE NEUROGENIC BLADDER

ERNEST BORS

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The reciprocal innervation of the smooth vesical detrusor muscle and of the striated muscles of the pelvic floor is well known, but it is not known whether the vesical mucosa is reflexly linked with the detrusor and pelvic floor muscles. The existence of such reflexes was reported in detail elsewhere.[1] This presentation deals with the practical application of vesical mucosal spinal reflexes.

In our previous investigation on paraplegic patients, stimulation and anesthesia of the vesical mucosa with ice water and pontocaine were done and the responses of the detrusor and pelvic floor musculature were recorded by means of sphincterometry and cystometry, by electromyography of the anal sphincter and by determination of bladder function with capacity residual tests. The sphincter ani was selected as a representative of the pelvic floor musculature and a significant participant in the bulbocavernosus reflex which is an important indicator of somatomotor activity of the conus medullaris. Ice water has been found to be a potent mucosal stimulus and indicator of visceromotor activity of the conus medullaris in patients with upper motor neuron lesions.

Two direct reflex arcs were reported (fig. 1): one from mucosal receptors to the sphincter ani (viscero-somatormotor) and the other from mucosal receptors to the detrusor (viscero-visceromotor). In addition, it was thought that the mucosal receptors were also involved indirectly by a feed-back mechanism in the following reflex arcs: Detrusor-detrusor, pelvic floor-pelvic floor, detrusor-pelvic floor, and pelvic floor-detrusor. The direct reflex arcs were called exteroceptive because the afferent impulses originate in mucosal receptors, while the indirect reflex arcs were called proprioceptive because their afferent impulses started in the musculature of the detrusor and pelvic floor, respectively. The exteroceptive arcs were believed to have a modulating effect upon the proprioceptive arcs and upon themselves, the latter became apparent from the fact that stimulation or anesthesia of the mucosal receptors changed responses of the bulbocavernosus reflex.

MATERIAL AND METHODS

One hundred twenty-four patients with spinal cord lesions were treated, 112 had traumatic cord damage at various levels of the neuraxis below C-5, and 12 had nontraumatic affections, such as multiple lesions, combined degeneration, tabes, tumor, radiculitis, and partial aplasia of the sacrum. One hundred twenty-one patients had upper and three patients had lower motor neuron lesions.

Read at annual meeting of Western Section of American Urological Association, Seattle, Wash., May 27–30, 1957.

[1] Bors, Ernest, and Blinn, K. A.: Spinal reflex activity from the vesical mucosa in paraplegic patients. A.M.A. Arch. of Neurol. & Psychiat., 78: 339–354, 1957.

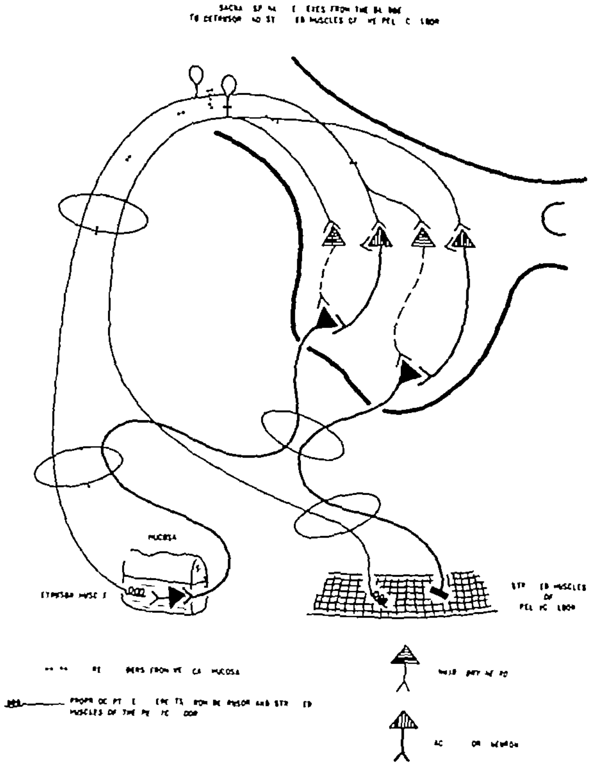

FIG 1 Sacral spinal reflexes from bladder to detrusor and striated muscles of pelvic floor *(A M A J Neurol & Psychiat , 78 339-354, 1957)*

Prior to the instillation of 2 or 3 ounces of a ¼ per cent aqueous solution of pontocaine, the residual urine and capacity of the bladder were determined The pontocaine remained in the bladder for 10 minutes and was then drained Another residual-capacity test was done after one hour, and again after 24 hours The type of voiding was observed, whether by reflex, extrinsic pressure (abdominal or manual) or a combination of both The fluid intake was regulated by giving the patient one glass of water every hour during waking hours

RESULTS

Of a total of 124 patients, 35 (28 per cent) responded so well to the procedure that they became catheter free, the results were good in 29 (26 per cent) of the 112 traumatic cases and in 6 (50 per cent) of the 12 nontraumatic cases

Since our first report of 36 patients, an additional series of 88 patients was studied, composed of 78 cases of traumatic and 10 cases of nontraumatic origin Twenty-five (32 per cent) of the traumatic cases and 4 (40 per cent) of the nontraumatic cases became catheter free, i e , a total of 29 (33 per cent) patients, while two additional patients showed so much improvement that the catheter could be temporarily removed The level or the extent of the lesion was irrelevant in regard to the result in the cases with traumatic lesions

Among these 88 patients, the bladder balance became temporarily good in 36 (41 per cent), became worse in 9 (10 per cent), complete retention remained unchanged in 21 (24 per cent), and a mixed response, i e , improvement or worsening of the bladder balance on repeated treatments, occurred in 23 (26 per cent) patients

Voiding by reflex contraction of the detrusor occurred in 40 (45 per cent) patients, by a combination of reflex and extrinsic pressure in 10 (11 per cent) by exclusive extrinsic pressure in 12 (14 per cent), and a varying type of voiding on repeated examinations in 5 (6 per cent) patients Twenty-one (24 per cent) patients failed to void at all

The capacity increased in 28 (32 per cent) patients, decreased in 32 (35 per cent), remained unchanged in 2 (2 per cent), was varying on repeated examinations, i e , increased or decreased, in 23 (26 per cent), and was not determined in 3 (3 per cent) patients

Thirty-four patients in this series of 88 underwent, on different occasions, topical pontocaine, pudendal and sacral nerve anesthesia The best response was observed in 10 (29 per cent) with topical pontocaine, in 6 (18 per cent) with pudendal, and in 8 (23 per cent) with sacral anesthesia Equal responses were achieved in 8 patients with pontocaine and pudendal nerve anesthesia, and in 6 with pontocaine and sacral anesthesia

Twenty-five patients in this series of 88 underwent one or two transurethral resections of the vesical neck with prior and subsequent pontocaine anesthesia In seven of the 23 patients with traumatic lesions, a permanent good bladder balance resulted after resection and following topical anesthesia, while the two patients with nontraumatic lesions did not respond to the treatment Transurethral resection with subsequent pontocaine anesthesia is thus responsible for 7 (8 per cent) of the 29 (33 per cent) patients with good permanent bladder function within the series of 88 patients

DISCUSSION

A beneficial effect of pontocaine anesthesia was obtained in 35 (28 per cent) of 124 cases This is a better result than was observed in our previous study when only 6 cases became catheter free Making allowance for the facts that bladder training was used, and that spontaneous establishment of bladder function is occasionally sudden, the striking evidence remains that the same bladder, when tested before anesthesia, did not function but did so after pontocaine instillation In some instances this happened after only one treatment

The mechanism of the effect consists of a reduction of mucosal impulses which leads to the removal of over-facilitation and, therefore, to relaxation of the pelvic floor musculature, so that an equilibrium between expulsive and retentive forces is created One must presume that in those cases which respond equally well to pontocaine and pudendal nerve anesthesia, the exteroceptive and proprioceptive impulses are of about equal magnitude in regard to the delicate balance in the spinal cord In the instances in which mucosal and sacral nerve anesthesia had a similar effect, perhaps the combined extero- and proprioceptive afferent impulses in the sacral nerves were of greater importance than merely the efferent to the pelvic floor, because pudendal anesthesia had failed

The effect of mucosal anesthesia was superior to that of sacral nerve anesthesia which was, in turn, superior to that of pudendal anesthesia, in the 34 cases in which all three methods were used This fact, together with the observation that even two patients with lower motor neuron lesions responded favorably to topical anesthesia, suggests that in addition to the sacral mucosal reflex arcs, similar lumbar mucosal reflex arcs exist, impulses from the mucosal receptors would then be recruited by the lumbar spinal cord into an efferent outflow to the lissosphincter of the bladder

This problem needs further study, because, if correct, it would also extend the scope of the mechanism of pontocaine action in cases with upper motor neuron lesions Inasmuch as the sacral and lumbar afferents carry stimuli from mucosal receptors, it would seem likely that a combined relaxation of the lisso and rhabdosphincters may result from this interruption of the afferent limbs of the reflex arcs, thus the numerically better effect could be understood which follows topical anesthesia in comparison with the other two methods, i e , pudendal or sacral nerve anesthesia, which act only upon the sacral reflex arcs This view receives further support by the observation that topical anesthesia is beneficial following transurethral resection of the vesical neck, when this alone was insufficient to establish bladder function by reducing the muscular power of the lissosphincter A similar experience has been made with the combination of transurethral resection and pudendal anesthesia However, there is this difference that pudendal anesthesia causes only relaxation of the cloacal part of the pelvic floor muscles while topical anesthesia relaxes the entire musculature of the pelvic floor, including its caudal part, i e , the levator and coccygeal muscles

Among 88 patients, topical anesthesia caused a temporary, balanced bladder function in 41 per cent, but a permanent one in only 33 per cent Unfortunately, anatomical conditions preclude a surgical attack upon the mucosal afferents in contradistinction to pudendal or sacral nerve procedures Therefore, there is no way of converting a temporary into a permanent good result

The type of voiding among 88 patients was preponderantly reflex, which confirms the previously reported observations on cystometry that autonomous and reflex contractions of the bladder are not altered by topical anesthesia although the tone decreases

There remains a wide field of open questions such as Why did 24 per cent of the 88 patients fail to respond to topical anesthesia? Why did topical anesthesia have an unfavorable effect on 10 per cent of the cases? Why was the effect favorable at one time but unfavorable at another, in 25 per cent of the patients? These problems merit further investigations So far, only few attempts have been made, and fewer yet were successful to combine topical with pudendal anesthesia, and none has been made to combine sacral with topical anesthesia, yet, it seems logical to embark on such ventures on theoretical grounds Sacral anesthesia attacks the detrusor and striated muscles of the pelvic floor, but does not alter the hypothetical lumbar reflex arc of the lissosphincter The effect of pudendal anesthesia is confined to the proprioceptive afferents and efferents of the cloacal part of the pelvic musculature, while additional topical anesthesia affects reflexly also the caudal part of this muscle group and possibly the lissosphincter Therefore, such combined methods may eliminate indirectly inhibitory impulses on micturition if they emanate from combined exteroceptive and proprioceptive over-facilitation of both sphincters

SUMMARY

Topical mucosal anesthesia of the bladder with two or three ounces of a ¼ per cent aqueous solution of pontocaine for 10 minutes, is a simple office procedure

This method established or restored bladder function in 28 per cent of 124 patients, of whom 112 had traumatic and 12 had nontraumatic spinal cord lesions

Primarily devised for the treatment of patients with upper motor neuron lesions, it may also benefit cases with lower motor neuron lesions

It was found to be of value in seven of 25 patients with a preceding transurethral resection of the vesical neck, which alone did not establish bladder function

Various theoretical aspects of the method are discussed in the light of past and present experience, and based upon these theories, combinations of topical anesthesia with pudendal and sacral nerve anesthesia are proposed for future study ceptive afferent impulses in the sacral nerves were of greater importance than merely the efferent to the pelvic floor, because pudendal anesthesia had failed

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SUMMARY

Topical mucosal anesthesia of the bladder with two or three ounces of a 1/4 per cent aqueous solution of pontocaine for 10 minutes is a simple office procedure

This method established or restored bladder function in 28 per cent of 124 patients, of whom 112 had traumatic and 12 had nontraumatic spinal cord lesions

Primarily devised for the treatment of patients with upper motor neuron lesions it may also benefit cases with lower motor neuron lesions

It was found to be of value in seven of 25 patients with a preceding transurethral resection of the vesical neck which alone did not establish bladder function

Various theoretical aspects of the method are discussed in the light of past and present experience and based upon these theories combinations of topical anesthesia with pudendal and sacral nerve anesthesia are proposed for future study

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UROLOGICAL COMPLICATIONS OF STROMAL ENDOMETRIOSIS

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Stromal endometriosis is of direct interest to the urologist because it produces ureteral obstruction and invades the bladder Although not previously stressed in urological literature, this neoplasm is being diagnosed with increasing frequency by those pathologists and surgeons who are aware of its existence

Stromal endometriosis is a type of primary uterine neoplasm whose infiltrative growth into the parametrial areas secondarily involves other pelvic viscera The histological appearance is one of endometrial stroma This neoplasm was first reported by Doran and Lockyer[1] in 1908, but universal recognition of it as a distinct clinico-pathological entity has been delayed both by a confusing nomenclature, and by a disputed histogenesis[2] Hunter's[3, 4] recent classification of stromal endometriosis has focused attention, not only upon recognition of this neoplasm, but on the involvement of the urinary tract and the possibility of successful surgical extirpation The purpose of this present communication is threefold to briefly discuss stromal endometriosis, to review all reported instances of its urinary tract involvement, and to present a case report of recurrent stromal endometriosis treated by anterior pelvic exenteration and uretero-ileal urinary diversion

CLINICAL AND PATHOLOGIC ASPECTS OF STROMAL ENDOMETRIOSIS

Stromal endometriosis would seem to be a relatively uncommon neoplasm, for a survey of the medical literature reports the existence of only 102 such cases[1, 31] This does not reflect its true incidence Prior to 1940 only five cases were reported, but, since 1950, the diagnosis of this tumor has been mentioned in the literature 51 times Analysis of the reported cases shows that it has been frequently misdiagnosed as myosarcoma and endometrial sarcoma An active interest in its existence has likewise affected its reported incidence, for Hunter and his associates have collected and reported 20 per cent of all the cases known to exist[3, 4, 8]

The majority of women so afflicted are in the second half of their reproductive life The presenting complaints include those of menometrorrhagia, abnormal noncyclic uterine hemorrhage, postmenopausal vaginal bleeding, pelvic pain,

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Read at annual meeting of Western Section of American Urological Association, Seattle, Wash , May 27–30 1957

[1] Doran, A H G and Lockyer, Cuthbert Two cases of uterine fibroids showing peri epitheliomatous changes Proc Roy Soc Med , **2** 25, 1908

[2] Pedowitz, Paul, Felmus, L B and Grayzel, D G Hemangiopericytoma of the uterus Am J Obst & Gynec **67** 549, 1954

[3] Hunter, W C Benign and malignant stromal endometriosis Surgery, **34** 258 1953

[4] Hunter, W C , Nohlgren, J E and Lancefield, S M Stromal endometriosis or endometrial sarcoma Am J Obst & Gynec , **72** 1072, 1956

and lower abdominal tumefaction The one most constant physical finding on examination is that of a symmetrically enlarged uterus [5]

The macroscopic pathological features of this neoplasm are characteristic and distinguishable from adenomyosis and ectopic endometriosis In the enlarged uterus diffuse infiltration of the myometrium will be evident as cord-like masses which are not demarcated by a true or false capsule Neoplastic growth near the endometrial surface produces an intrauterine polypoid growth in about 45 per cent of these tumors [5] Freshly cut sections of tumor have a yellowish-white color and a distinctive "rough towel" or "comedo" appearance This is due to multiple, pouting white ends of tumor cords which are elevated above the surrounding surface and have a peculiar elastic resiliency Extrauterine spread on palpation gives a typical sensation of "rubbery worm-like cords" due to intravascular permeation of tumor tissue With traction, these cords of tumor stretch like rubber bands, and, if removed, their channels remain open as patulous smooth-walled tunnels With involvement of the urinary bladder, adnexa, bowel, and peritoneum, multiple firm nodules of a yellowish color are usually seen on the serosal surface Cyst formation is not infrequent and occurs with infiltration of ovarian tissue

Histological examination reveals infiltration of the surrounding normal tissues by discrete tumor columns of solid cellularity These cells are round or spindle-shaped with poorly defined cytoplasmic borders They bear a resemblance to midcyclic endometrium Leptochromism is a prominent feature of the nuclei which have a uniformity of rounded contour and size Mitoses are uncommon The vascularity of this tumor is marked by the presence of numerous arteriolar-like blood vessels as well as capillaries For this as well as for other reasons, some investigators have teleologically proposed that this neoplasm is dependent upon its own uterine blood supply for nourishment and growth [6] Invasion of endothelial-lined channels is usually seen in extrauterine spread, but identification of these channels as veins or lymphatics is rarely possible Stromal endometriosis can be differentiated from endometrial sarcoma by the use of reticulum stains In stromal endometriosis the wavy collagenous fibers enmesh each individual cell in a so called "basket-weave" pattern, which is often hinted at by the use of ordinary staining techniques

HISTOGENESIS

The term, stromal endometriosis is enigmatic and the obscurity surrounding its cellular derivation from endometrial tissue has led to a number of synonyms stromatous endometriosis,[3, 25] endolymphatic stromal myosis,[10, 27] endometrial sarcoma,[12, 14, 24] endometrioma interstitiale,[30] endometrial sarcoid,[20] and stromatoid mural sarcoma [22] These various synonyms attempt to describe the histological structure or depict the cellular derivation Hunter[4] has proposed the concept that stromal endometriosis is a peculiar neoplastic variant of adenomyosis, while Goodall[7] believes that it is a different form of endometriosis An entirely different cellular origin has been suggested by Park[5] who believes that this tumor grows from undifferentiated mesenchymal and epithelial cellular residuum of the embryonic genital canal An additional postulate by Embrey[8] is that this neoplasm is actually an overgrowth of heterotopic tissue which has abnormally differentiated While conceptually diverse, the above authors do agree that the basic origin of this neoplasm is from endometrial tissue or its embryonic precursor The one opposing concept is that of Pedowitz,[9] who believes that this neoplasm actually has its origin in vascular tissue and has, therefore, classified this tumor as a hemangiopericytoma

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[5] Park W W The nature of stromatous endometriosis J Obst & Gynaec Brit Emp, 56 755 1949

[6] Hill, J H Fibromyosis uteri Endometrial type Arch Path, 43 527, 1947

EXTRAUTERINE STROMAL ENDOMETRIOSIS

The ready tendency of stromal endometriosis to infiltrate in and along lymphatic and vascular channels has led to surgical resections that are either inadequate or deliberately palliative The tumor residuum remaining in the parametrial areas or in the cervix after subtotal hysterectomy infiltrates initially the tissues and organs of the pelvis With such recurrence patients complain of pelvic discomfort and of pressure from tumor growing up into the lower peritoneal cavity Colostomies have been performed in numerous instances to relieve rectal and sigmoidal obstruction Vaginal infiltration by stromal endometriosis is almost universal with production of foul discharge and hemorrhage The remaining ovarian tissue may likewise be involved by solid or cystic tumor Vascular stasis of the lower extremities results from both extrinsic tumor pressure and actual tumor invasion of the pelvic veins The lower urinary tract is invaded diffusely and extensively Incontinence, dysuria, urgency, frequency, hematuria and uremia have been noted Extrauterine neoplasm is predominantly and essentially a local infiltrative process although distant metastatic spread to the lungs has been reported in three instances[4, 7]

The attendant morbidity and mortality of stromal endometriosis is a function of involvement of anatomically vital sites, rather than of neoplasm per se The recurrence of tumor from residuum is neither invariable, nor necessarily rapid In a series of four palliative resections with tumor residuum by Henderson,[10] three were alive and well six to nine years later with the single mortality occurring during the fifth postoperative year From all the cases of stromal endometriosis mentioned in the medical literature, 82 detailed reports are available for analysis Statistical conclusions of morbidity, mortality, extrauterine spread, and recurrent growth are not presented because the great majority of detailed case reports have undergone observation periods of less than three to four years with exceptionally few deaths There are reports of 15 patients who have survived for more than nine years[2 5 7 9 10 14 15 17 18 23 25] Hunter[4] has reported three patients who survived 19, 22, and 26 years respectively after the initial surgery of hysterectomy The one patient who survived 26 years had four separate recurrences of tumor growth and her last successful surgical procedure was 19 years after the initial diagnosis Stress should therefore be placed on the observation that stromal endometriosis, even with extrauterine infiltration and distant metastasis, is essentially a benign neoplasm

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[7] Goodall, J R A Study of Endometriosis Endosalpingitis, Endocervicosis and Peritoneo Ovarian Sclerosis Philadelphia J B Lippincott Co , 1943, chapts 2 8 9 and 10

[8] Embrey, M P Stromatous endometriosis J Obst & Gynaec Brit Emp 59 846, 1952

[9] Pedowitz Paul Felmus I B and Grayzel D M Malignant vascular tumors of the uterus Am J Obst & Gynec , 69 1309 1955

[10] Henderson N D Endolymphatic stromal myosis Am J Obst & Gynec 52 1000 1946

The histological structure of extrauterine growth tends to be identical to the initial cellular appearance of the primary neoplasm The histological and cellular structure bears no relationship to the time of recurrence and the duration of the disease In some patients this neoplasm seems to have a limited growth potential and foci of clinically evident tumor may remain stationary for long periods of time It is likewise true that these same patients may tolerate the presence of even large amounts of tumor with few or no symptoms Prognosis, therefore cannot be measured by either the macroscopic characteristics of this tumor or by the histological structure

URINARY TRACT INVOLVEMENT

The involvement of the urinary tract occurs in those patients with extrauterine infiltration of stromal endometriosis Though previously considered rare, macroscopic involvement of the urinary tract has been reported as approximately 12 per cent of all cases reviewed Five such instances[4 7 11] are well docu-

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[11] Present communication

[12] Corscaden J A Sarcoma of endometrium Am J Obst & Gynec 61 743, 1951

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[14] Wheelock M C and Strand, C M Endometrial sarcoma Obst & Gynec, 2 384, 1953

[15] DeCarle, D W So-called endometrioma interstitiale West J Surg, 53 48, 1945

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[28] Robertson Thomas Hunter W C Larson P and Snyder G A C Benign and malignant stromal endometriosis Am J Clin Path 12 1 1942

[29] Symmonds R E and Dockerty M B Surg Gynec & Obst 100 232 1955

[30] Goodall J R Endometrioma interstitiale J Obst & Gynaec Brit Emp 47 13 1940

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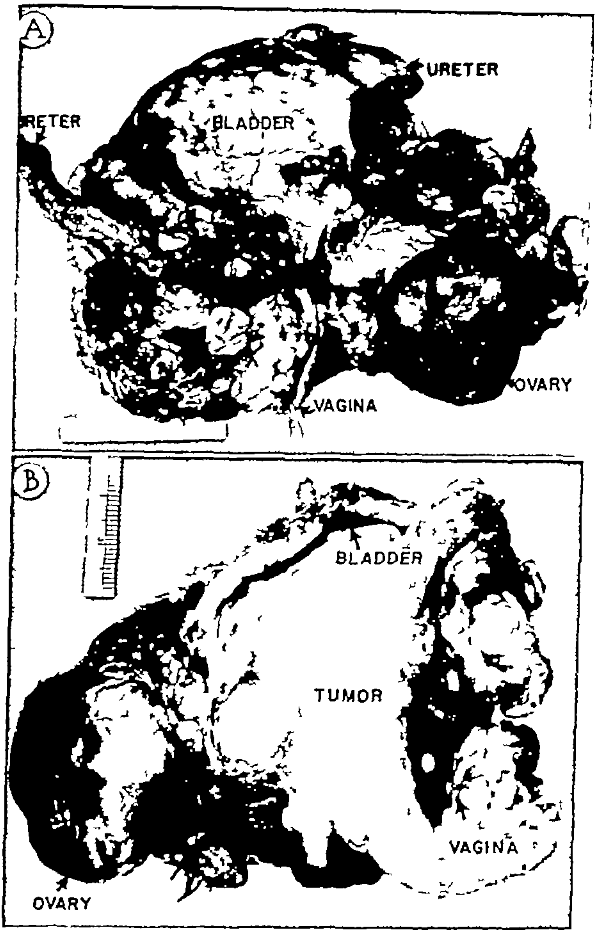

FIG 3 *A*, surgical specimen shows entrance of both ureters in solid nodular areas of neoplasm Polypoid infiltration of bladder is present as well as neoplastic replacement of left ovary *B*, cross section of specimen shows nodular neoplastic infiltration into vagina and bladder

On September 17, 1956, an exploratory laparotomy was performed The large left ovarian cyst had one area of solid tumor within its wall The peritoneal cavity itself was free of neoplastic infiltration and there was no encroachment upon the sigmoid colon Tumor had involved both parametrial areas with extension to but not into the pelvic musculature on the right The anterior vaginal wall and vesical floor were grossly thickened Tumor was also palpable within the dome and fundal areas of the bladder wall itself, and a yellowish subserosal nodule of tissue was present on the bladder fundus The right ovary was replaced by a solid tumor mass measuring approximately 4 by 5 cm The downward course of both ureters ended in solid neoplasm with marked dilatation on the left

Anterior pelvic exenteration was performed, and urinary diversion was ac

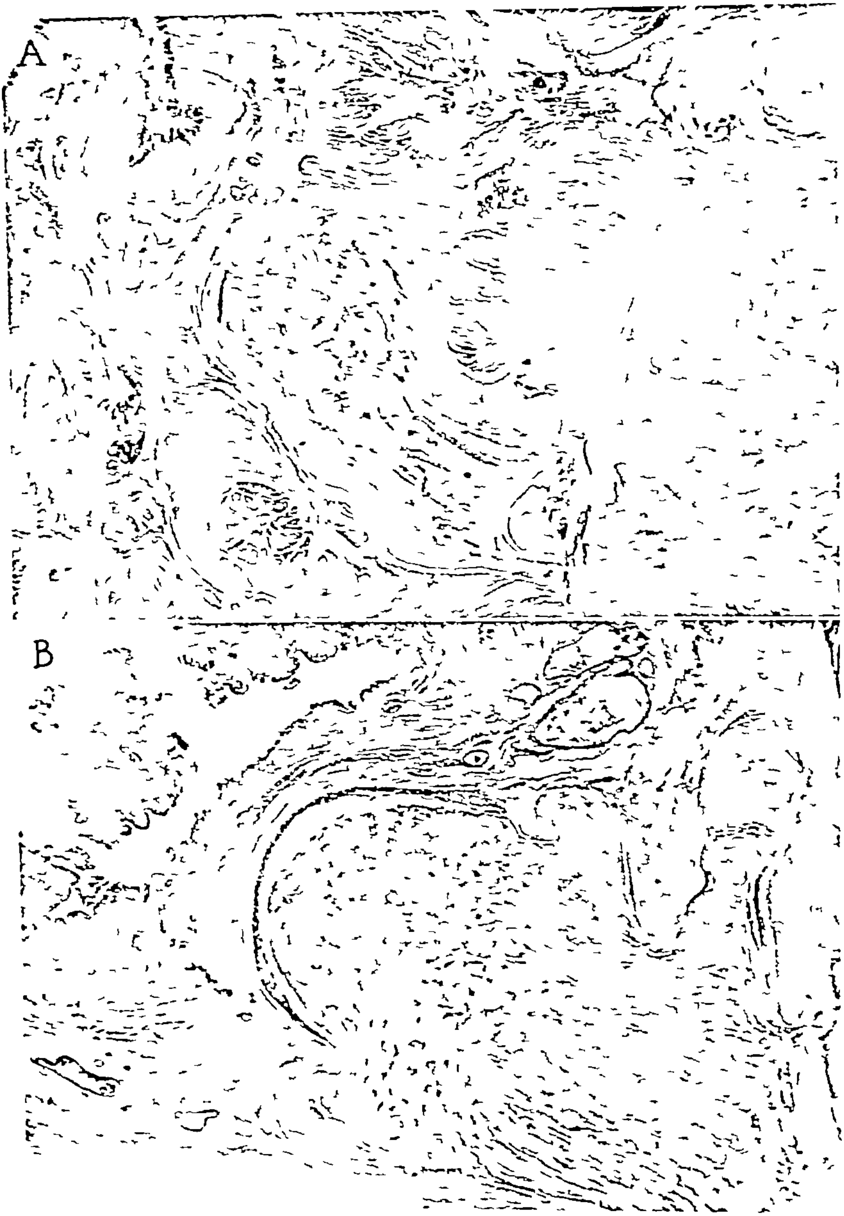

FIG 4 A, invasion of bladder by stromal endometriosis Note discrete cords of tumor invading muscularis (× 25) *B*, similar invasion of ureteral wall by neoplasm Note marked vascularity (× 25)

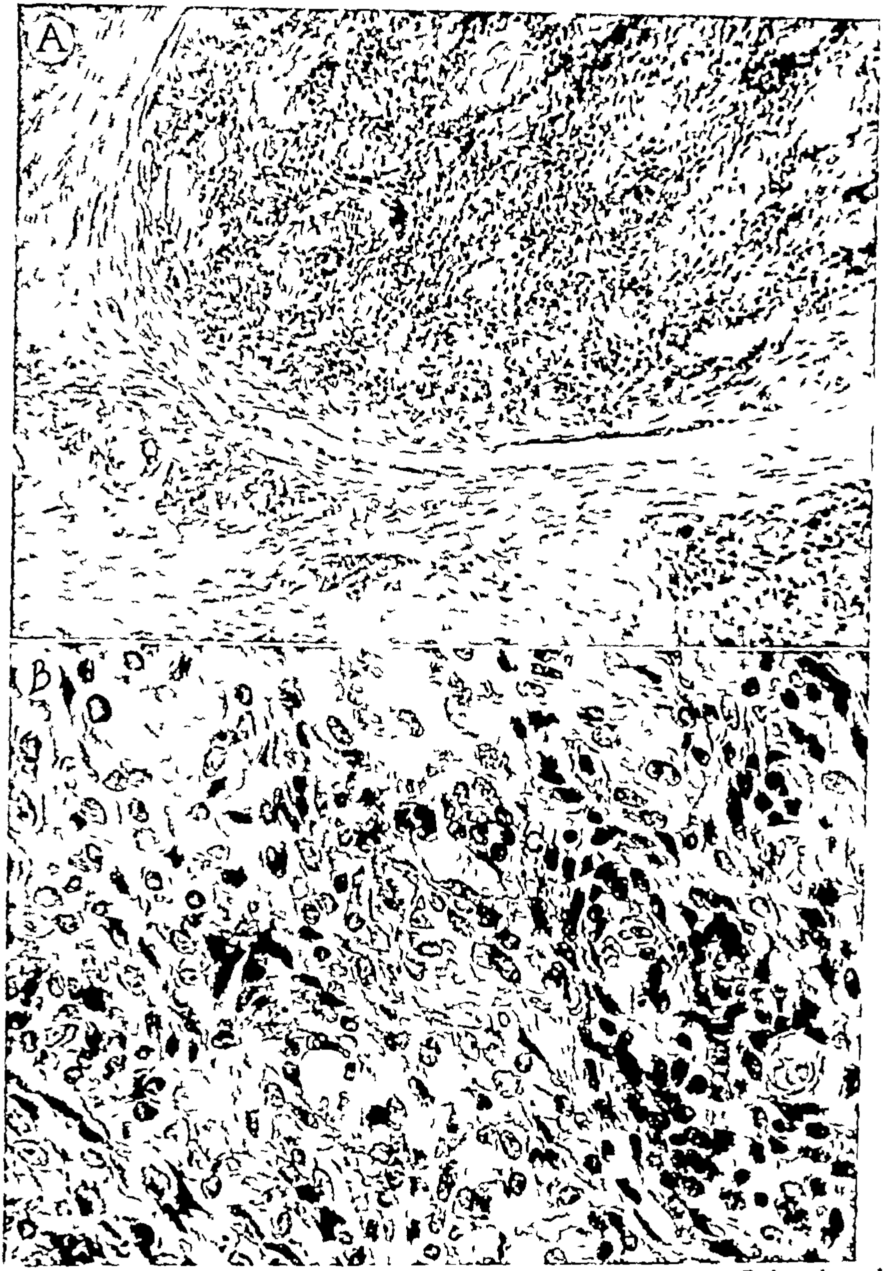

Fig 5 *A*, permeation of endothelial lined channel by tumor (× 160) *B*, histological structure of stromal endometriosis Cytoplasmic borders are indistinct but nuclei are uniform in size and staining properties Shown are several arteriolar like blood vessels complished by means of bilateral ureteral transplants into an isolated ileal conduit with a cutaneous ileostomy No technical difficulties were encountered during surgery Her subsequent course through the end of the seventh postoperative month has been one of marked clinical recovery The serum electrolytes are normal The ileal conduit functions well Blood urea nitrogen is 23 intravenous pyelograms show prompt function, and gratifying improvement in the morphology of the renal collecting systems (fig 2)

On examination, the surgical specimen weighed 715 gm minus the fluid contents of the ovarian cyst Identified in the neoplastic mass was the urinary bladder, the distal portions of the ureters urethra, a greater portion of the vagina, and both ovarian masses On macroscopic examination of the specimen, Dr Warren C Hunter noted that a shiny subserosal, yellowish polyp was present at the base of the urinary bladder There was ropy, nodular infiltration of the vesical wall, and the entire bladder floor was irregularly lobulated due to whitish protrusions of tumor which were contiguous with the infiltration into the anterior vaginal wall The ureteral orifices could not be identified Though the ureters were completely obstructed by tumor, direct intraluminal ureteral invasion was not present Section of the solid tumor disclosed multiple soft, white bodies which protruded slightly above the surrounding surface (fig 3)

Histologically the tumor cells were of a spindle shape and had nuclei which were uniform in size and staining properties Wavy collagenous fibers were seen to enmesh the individual cells which lay in discrete clumped masses Cords of tumor also lay within blood vessels and in the bladder wall there was tumor interruption and displacement of muscle bundles, as well as involvement of the submucosa Numerous small blood vessels with appreciable walls were evident in the areas of neoplastic infiltration (figs 4 and 5)

Diagnosis Recurrent stromal endometriosis involving bladder ureters, vagina and ovaries as well as the surrounding pelvic supporting tissues

COMMENT

Stromal endometriosis is undoubtedly a more common entity than the number of reported cases would indicate Fewer myomectomies and subtotal hysterectomies will be done as the knowledge of stromal endometriosis is disseminated Its natural history indicates the desirability of radical excision of extrauterine spread in patients who previously had only exploratory laparotomies It can be said that stromal endometriosis is a slow-growing neoplasm with benign histological characteristics which become malignant by physical occupation of vital anatomical locations in the female pelvis This results in obstruction of the urinary system the lower bowel, and/or the pelvic vasculature Its infiltration of the internal genitalia is distressing but not necessarily lethal Even in extensive extrauterine infiltrations, producing the so called 'frozen pelvis' there may be a paucity of symptoms In far advanced stages pain is seemingly secondary to pressure effect, for neoplastic involvement of the pelvic and sacral nerves does not seem to be characteristic of this growth Painful bony skeletal metastases have likewise not been reported The slow growth potential of this tumor even in metastatic disease must be remembered Whether or not the term "malignant" can be applied to this neoplasm is not a consideration within the scope of this report

For these reasons, therapeutic considerations for the urologic care of these patients differ from the usual care of malignant extension from the female genital system

Total surgical excision is, at present, the only definitive and positive approach to predicable palliation and cure Initial total hysterectomy with careful exploration for, and resection of, extrauterine infiltrations is sound and correct The need of urological surgery is present in the more advanced stages of this tumor Here, not only may the floor of the bladder be invaded, but the obstructed ureters may lie solidly encased in neoplasm The procedure of choice will usually be urinary diversion and anterior pelvic exenteration to accomplish relief of obstructive uropathy, and removal of all affected structures The question of urinary diversion alone and also of total pelvic exenteration for concomitant rectal involvement must be left as an individualized decision

The urologist has a particular diagnostic advantage in his opportunity to view the tumor He is frequently consulted by the gynecologist regarding women with recurrent pelvic tumors and symptoms of bladder involvement The presence of bladder infiltration in such a patient with a slowly growing pelvic tumor should arouse clinical suspicion as to the possibility of stromal endometriosis Soft nodular elevations on the floor of the bladder and/or yellowish polypoid formations should also arouse diagnostic suspicion

SUMMARY

Stromal endometriosis is a primary type of uterine neoplasm which invades and obstructs the urinary tract It should not be confused with the non-neoplastic entities of adenomyosis and ectopic endometriosis The growth of stromal endometriosis is slow and its clinical course is one of benignity until obstruction of the urinary tract, the pelvic vasculature and the lower bowel occurs

This neoplasm with its urinary tract involvement has not heretofore been formally introduced into urological consideration A discussion of the clinical and pathological characteristics of this disease has been presented from material obtained in a review of all available reported cases in the medical literature The case report presented is of a patient with far advanced stromal endometriosis in whom anterior pelvic exenteration was performed with urinary diversion by ureteroileostomy This case report illustrates the usual characteristics of this disease and the surgical role of the urologist in relation to its treatment Major stress has been placed on the consideration of palliative urinary diversion and curative surgical extirpation

We wish to acknowledge appreciation to Dr Ronald W Philips for illustrative roentgenograms reproduced on the LogEtronics and also to Mr James T Phillips for the illustrations of microphotography

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TREATMENT OF RESISTANT CONTRACTURE OF THE BLADDER NECK IN WOMEN BY PLASTIC REVISION OF THE VESICAL ORIFICE

DAVID FALK

The surgical modalities for the relief of ' vesical neck contracture in women are largely unsatisfactory This study was undertaken in an attempt to improve upon results obtained by other surgical methods

REVIEW OF LITERATURE

Surgical methods applicable to the relief of bladder neck obstruction fall into two main categories transurethral and retropubic or perineal An excellent inclusive review of the transurethral technique was presented by Nelson and associates[1] They report that following surgery half of their patients were without symptoms and the other half retained symptoms of varying degrees of severity Young and Goebel[2] Lich and Maurer,[3] and Burns[4] have reported their experience with the open (retropubic) method of vesical neck revision in the treatment of vesical neck stenosis in children To my knowledge, the retropubic approach to vesical neck revision in the adult female has not heretofore been reported Hock[5] describes a vaginal approach for the relief of obstructive factors external to the bladder and urethra

INDICATIONS FOR SURGERY

The indications for the surgical treatment of vesical neck obstruction in the adult female are not clearly outlined In this study each patient had a complete urological study and was carefully observed for a minimum of four months before surgery was advised Surgery was recommended if prolonged continuous therapy by conservative methods (vesical neck dilation vesical irrigation vesical distention medications) failed to give relief for at least one month s duration from the symptoms of obstruction infection frequency, urgency and nocturia

The objective criteria were of less importance in the surgical decision than the subjective Cystoscopic findings are too variable to utilize as an indication for surgery The ' collar contracture, as noted by Nelson and associates[1] is an objective finding but does not necessarily denote stenosis of the vesical neck These authors clearly state, 'The discovery of a collar contracture of the vesical neck is not an indication in itself for transurethral resection The other objective findings of importance were persistent residual urine infected or uninfected, and recurrent acute cystitis

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Read at annual meeting of Western Section of American Urological Association Seattle Wash May 27-30 1957

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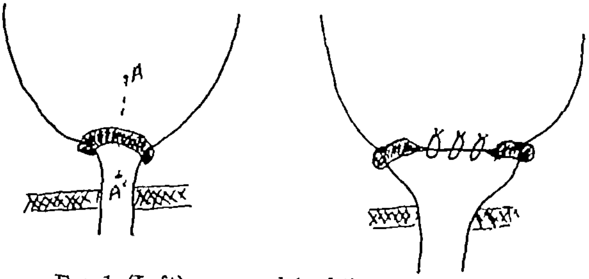


FIG 1 (Left), pre- and (right) postoperatively

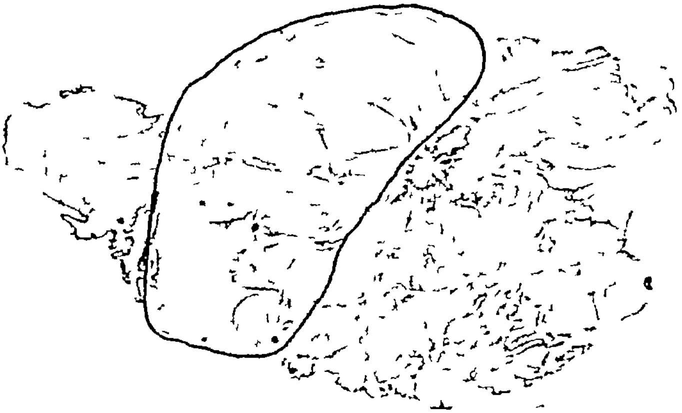


FIG 2 Cross section of ring like sphincter

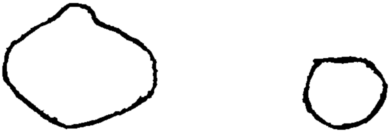


FIG 3 Cystoscopic appearance of vesical orifice (oblique lens) (Left), pre and (right) postoperatively

SURGICAL METHODS

The bladder is approached suprapubically and opened for the examination of the vesical orifice by palpation and direct inspection The urethroplasty is then made (fig 1) Specimens for pathological study are removed from the anterior and posterior vesical neck at the sites of repair

One surgical procedure was done upon the vesical neck at the time of a cystocele repair The posterior vesical orifice was cut longitudinally in the midline and repaired transversely The wound healed perfectly with no fistula formation

PREOPERATIVE AND POSTOPERATIVE FINDINGS

In each patient, the bladder neck was found to be tightly contracted with a rigid, elevated, thickened, almost cartilage-like posterior lip In some cases considerable force was necessary to insert the tip of a finger through the contracted orifice This was particularly so in those cases which had previously been subjected to transurethral resection

After the revision had been performed and the posterior vesical neck excised, the new vesical orifice appeared widely open The examining finger within the bladder passed through the wide-open vesical neck and met the first sense of resistance at the urogenital diaphragm where this encircled the urethra In each case an adequate reduction of the obstruction appeared to have been accomplished

The urethrovesical juncture was examined carefully in cross-section at the time of the anterior longitudinal incision In each case there was a definite thickening of the tissue at this point, forming a more or less well defined ring This ring-like area was often dense and resistant, cutting with a gritty sensation During repair care was taken to separate the ends of this band widely in the transverse closure In one case a very definite, well demarcated ring-like sphincter was found to extend around the circumference of the urethrovesical juncture Figure 2 shows the microscopic nature of this ring from a cross-sectional aspect

Cystoscopic findings after the revision are diagrammatically represented in figure 3

Following repair, the anterior portion of the vesical orifice appeared wide, dome-like and not constricted Posteriorly, where a segment had been taken from the vesical orifice, a notch connected the trigone and distal urethra The posterior vesical lip appeared soft and flat As far as could be determined from cystoscopic examination, the vesical orifice appeared to be of greater circumference when viewed postoperatively than it did when viewed preoperatively

In no instance did incision of the ring-like dense anterior vesical orifice release the tight, rigid posterior vesical lip

RESULTS

Nine patients ranging in age from 23 to 64 years were treated Eight were operated upon by the suprapubic approach, one by vaginal approach during cystocele repair One patient of this series underwent vesical neck surgery at the time of oophorectomy for a benign ovarian cyst Excellent relief of her bladder symptoms was obtained for 10 months, when symptoms reappeared Vesical neck dilatation, which previously had afforded little relief, now is the only treatment which will relieve her bladder symptoms completely

Six patients had some relief varying from good to fair for from one to four months After a year of postoperative followup, none has obtained any lasting benefit, and none is responsive to conservative methods of therapy

Two patients obtained no relief whatsoever and are no better, if not worse, following surgery These two patients were subsequently subjected to transurethral resection of the bladder neck with no beneficial result These patients are unresponsive to any method of therapy in use at the present time

There were no complicating factors such as urinary fistula or incontinence in this series

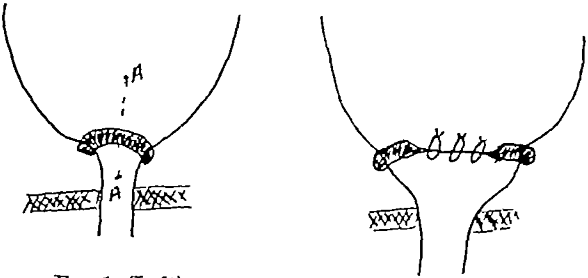


Fig 1 (Left), pre- and (right) postoperatively

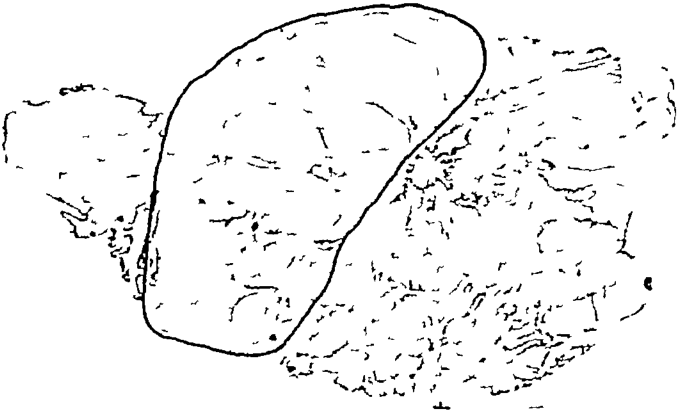
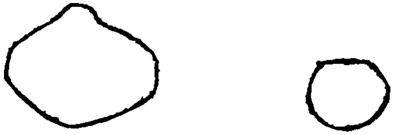


Fig 2 Cross section of ring like sphincter



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PATHOLOGY

Histopathological study of the tissue removed is comparable with that reported by Nelson and associates[1]

CASE REPORTS

Illustrative case histories are presented

Case 1 O H , a 23-year-old white woman, had had symptoms of vesical irritation and recurrent urinary tract infection since early childhood Vesical symptoms were greatly aggravated following marriage In September 1951 the patient experienced acute urinary retention and severe cystitis following delivery of her first child Urological study at that time was reported as "negative "

In January 1953 the patient complained of constant lower abdominal discomfort, lower abdominal fullness, "bearing down," perineal sensation and sensation of loss of perineal support She complained bitterly of dyspareunia consisting of severe urgency with frequency and dysuria for 24 hours following coitus "Exploratory laparotomy" was performed by the department of gynecology Uterine retroversion was found and a bladder suspension performed "Pelvic adhesions" were released A hydatid of Morgagni was removed from the right broad ligament Acute urinary retention and severe cystitis complicated the postoperative course The abdominal and urological complaints were the same following surgery

In August 1954 appendectomy was performed because of continuous right lower quadrant pain, a normal appendix was removed

In August 1955 the patient was first seen by the author The essential findings on urological study were mild trabeculation of the detrusor There was difference of opinion among the urological staff regarding cystoscopic evidence of bladder neck contracture Various types of therapy were applied but the greatest relief, lasting only four to seven days, was obtained from vesical neck dilatation

In May 1956 retropubic revision of the vesical orifice was performed The posterior bladder lip was thickened, quite rigid and elevated This was resected Following surgery the patient had moderate improvement for one month following which her symptoms returned Five months following surgery the patient had 150 cc infected residual urine Dilatation to size 36F resulted in relief of symptoms for one week's duration The patient refused further surgical therapy

This case illustrates the gynecological and surgical implications of the "bladder neck syndrome " It is not at all uncommon to see patients who have had multiple forms of gynecological surgery performed for symptoms arising primarily from a pathological process in the urinary tract

Case 2 Z T , a 48-year-old white woman, had had symptoms of obstructive uropathy, urgency and recurrent cystitis of one year's duration When first seen in February 1956, episodes of acute cystitis were occurring at three-week intervals and response to antibiotic therapy was diminishing in effectiveness

Examination disclosed 110 cc clear residual urine Cystoscopy revealed heavily trabeculated bands of detrusor muscle with hypertrophy of the interureteric ridge Marked contracture of the bladder neck was present, as well as elevation and thickening of the posterior lip when viewed cystoscopically

The only effective therapy was bladder neck dilatation to size 40F Excellent relief of symptoms was obtained but did not persist longer than 10 days Residual urine persisted despite all methods of treatment, and acute cystitis was recurrent

After four months of observation and treatment, retropubic revision of the vesical orifice was performed The bladder neck was contracted with moderate elevation and thickening of the posterior vesical lip

Postoperatively, the patient had relief of symptoms for one month, following which all urological difficulties reappeared Cystoscopy revealed the bladder neck to be flattened and soft posteriorly, and widely open Despite repeated dilatation of the bladder neck to size 12F, no relief was obtained In October 1956 transurethral resection of the bladder neck was performed and approximately 0 5 gm of tissue removed The posterior vesical lip was very thin and extreme caution was necessary to prevent perforation during resection Following transurethral resection there has been no relief of symptoms and no response to any therapy

Comment Although obstruction at the vesical neck appears to have been relieved, cure has not been obtained Multiple factors, other than obstruction at the vesical neck, must be studied and accounted for if success is to be expected

DISCUSSION

Critical analysis of the results obtained in this study reveals significant lack of our knowledge of vesical function in health and disease

The philosophy of procedure in this study was based upon obstruction, observed subjectively and objectively It would seem logical, therefore, that relief of the obstruction should result in cure But what is "obstruction?" Is it "spasm," is it "fibrous contracture," is it hypertrophy of the female prostate?" What is the order of its magnitude and how can it be measured? If we assume that obstruction was relieved, as it appeared, why did the procedure fail? What are the other variables and how must they be taken into account in planning a program of therapy?

Vesical function may be regarded as a dynamic system in which the forces of expulsion are equated with the forces of retention No completely integrated, accurate measurement of the forces involved in this interrelationship has ever been made The only logical approach to the problem, therefore, lies in establishing a sound scientific baseline of normal vesical dynamics This must be done before the abnormal can be measured and evaluated with objective scientific accuracy Hopefully, then, practical diagnostic and therapeutic modalities may be derived from these studies

A research program of this nature may well reach major proportions, involving considerable expenditure of time, effort and money There are two questions to be answered 1) Are the results to be obtained worth the effort? 2) How may such a program be most efficiently planned and directed?

The "bladder neck syndrome" is common to both sexes and all stages of life, in all its varied manifestations and degrees of involvement, and is the single most common urological disorder The problem of accuracy in diagnosis and treatment is largely an unsolved one Because of a wide variation in theory of causa-

PATHOLOGY

Histopathological study of the tissue removed is comparable with that reported by Nelson and associates[1]

CASE REPORTS

Illustrative case histories are presented

Case 1 O H , a 23-year-old white woman, had had symptoms of vesical irritation and recurrent urinary tract infection since early childhood Vesical symptoms were greatly aggravated following marriage In September 1951 the patient experienced acute urinary retention and severe cystitis following delivery of her first child Urological study at that time was reported as "negative "

In January 1953 the patient complained of constant lower abdominal discomfort, lower abdominal fullness, "bearing down," perineal sensation and sensation of loss of perineal support She complained bitterly of dyspareunia consisting of severe urgency with frequency and dysuria for 24 hours following coitus "Exploratory laparotomy" was performed by the department of gynecology Uterine retroversion was found and a bladder suspension performed "Pelvic adhesions" were released A hydatid of Morgagni was removed from the right broad ligament Acute urinary retention and severe cystitis complicated the postoperative course The abdominal and urological complaints were the same following surgery

In August 1954 appendectomy was performed because of continuous right lower quadrant pain, a normal appendix was removed

In August 1955 the patient was first seen by the author The essential findings on urological study were mild trabeculation of the detrusor There was difference of opinion among the urological staff regarding cystoscopic evidence of bladder neck contracture Various types of therapy were applied but the greatest relief, lasting only four to seven days, was obtained from vesical neck dilatation

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PLASTIC REPAIR OF EXSTROPHY OF BLADDER COMBINED WITH BILATERAL OSTEOTOMY OF ILIA

W G SHULTZ

So far as I am aware, this combination of procedures has never been attempted One case does not prove a rule, but the end result has been so successful that I must report it, in order that others of you who have had more experience with such patients may give it a trial, add improvements to the technique and develop procedures that will increase the number of satisfactory functional results

I had the good fortune to observe one of the excellent urologists in the country perform a plastic repair on such a case He severed the right arm of urethral sphincter muscle at its attachment to the right pubic bone, and brought this end over the to be constructed urethra, suturing it to the base of the left arm of urethral sphincter muscle He was tempted to perform the same procedure on the left, but did not do so because he believed that severing the attachment interfered with blood and nerve supply sufficiently that it might be responsible for failure to obtain a functioning urethral sphincter He then did a beautiful construction of the urinary bladder as well as a fascial sliding closure of the abdominal muscles over it The immediate end result was excellent but the future functional result was not

Therefore it occurred to me that if some procedure could be devised to bring the pubic bones together, the undesirable separation of the sphincter muscles from their pubic attachments could be avoided, and the fascial sliding closure of the abdominal muscles would likewise be unnecessary, resulting in marked simplification of both procedures and the possibility of a much more satisfactory end result

When the case herewith reported (fig 1) was referred to me by the Crippled Childrens Clinic, a local orthopedic surgeon, Dr John R Schwartzmann, was rendering orthopedic care When he learned that the patient was to be hospitalized by me for repair of the bladder exstrophy, he requested that I let him know when I had completed my surgical procedure, as he was desirous of performing an orthopedic surgical procedure and thus avoid readmission It was his intention to perform osteotomy of the ilia to correct external rotation of both hips and legs as well as correct the gait which was quite unstable When I inquired if this procedure would permit fairly close approximation of the two pubic bones he said that it would, and I suggested that he perform the osteotomy before I did any procedure and that, at the time of the bladder repair, a suitable interval after this osteotomy, we might be able to combine fixation of the pubic bones at a suitable point during the bladder reconstruction Such a procedure was decided upon

CASE REPORT

D K, aged 2½ years, was born with exstrophy of the bladder and prolapse of the rectum with incontinence of feces She was first seen by me December 6,

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Read at annual meeting of Western Section of American Urological Association, Seattle, Wash, May 27-30 1957 tion and therapy, I prefer to class the varied manifestations under the heading of the "bladder neck syndrome" This disorder can and does cause fatal renal destruction It is often disabling and a cause of economic loss Most often it makes life a constant misery for the millions of sufferers who are its victims Consider these nine sick, discouraged, helpless patients Add to them those patients in a similar predicament who are seen in doctors' offices throughout the world Even then, this is without consideration of the untold numbers who are undiagnosed, misdiagnosed, mistreated, maltreated and untreated They will pleadingly answer question number one

There are a number of possible approaches to question number two

It is proper to assume that the problem is primarily urological in all its implications A research program of this nature should be planned and operated under the supervision and control of trained urologists The logical body to assume such a task would be the American Urological Association, perhaps through a special research committee created for this particular purpose Financial support could be sought from the foundations which allocate funds for medical research

SUMMARY AND CONCLUSIONS

A new surgical technique, retropubic revision of the vesical orifice, was adopted and employed for the relief of resistant "contracture of the bladder neck" in adult females

Of nine patients treated by this method, none were permanently relieved and any benefit obtained was transitory

Critical analysis of the reasons for failure indicates a serious lack of knowledge of vesical dynamics in the normal and abnormal states

The "bladder neck syndrome" represents the most common urological disorder now in existence Basic research in the causes effects, diagnosis and treatment is necessary and warranted

2026 17th St , Bakersfield, Calif

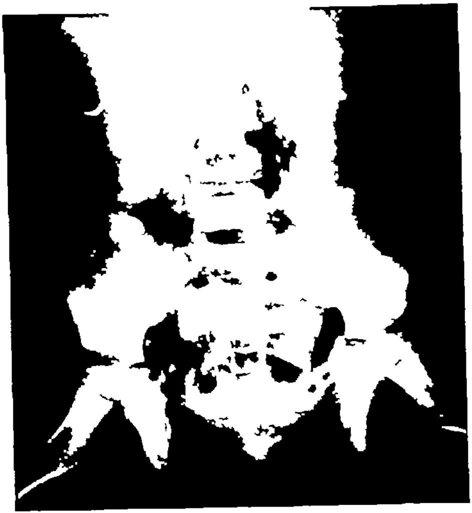

Fig 2 Intravenous pyelogram 10 days before operation Note wide external rotation of hips and wide separation of pubic bones

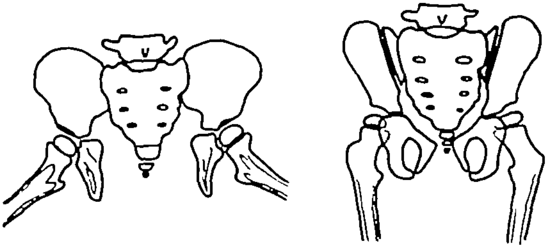

Fig 3 Tracing over x ray films shown in figures 2 and 5 Sites of osteotomies are clearly shown, also correction of external hip rotation as well as close approximation of pubic bones

ing this an attempt will be made to complete restoration of the symphysis pubis and restore a pelvic arch for this child " See figures 2 and 3

On March 4, I operated upon the patient Two incisions were made in the mucosa from the lower end of the trigone almost to the opening of the vagina, one on each side in such manner that an ⅛ inch strip of mucosa was left at the base where a urethra was to be constructed The mucosa was then incised over each sphincter muscle and flaps of mucosa laid back from each muscle so that they were denuded completely The bladder was then completely freed from the skin edges and also separated from peritoneum to the extent that it could be held as a cyst and depressed into the pelvic portion of the abdomen quite readily The skin edges were then dissected free from the abdominal muscles exposing them approximately one inch on each side Four strands of heavy vitallium wire were then laid in the midline over the strip of mucosa which had been left for a urethra These strands to serve as a urethral splint were long enough so that their upper ends could protrude through the suprapubic opening and their lower ends

1954 Two operative procedures had previously been done on the rectum The first was by an abdominal approach at which time a uterus, tubes, ovaries, as well as vagina were reported to be present An attempt to elevate the rectum was unsuccessful as to incontinence of feces A second operation, on the rectal sphincter at Childrens Hospital, was successful

The patient was admitted to St Mary's Hospital in February 1955 and on the eighteenth Dr John R Schwartzmann performed the osteotomy Operative report of Dr Schwartzmann "The patient has complete exstrophy and a congenital anomaly of the pelvis in that the pubic bones and the pelvic arch pass directly anteriorly from the sacroiliac joint and the symphysis lies about three inches apart This results in external rotation of the hips and the child walks with a waddling gait, grossly unstable on both sides although the hips themselves are in joint Dr Shultz has examined the child and plans to repair the bladder, returning it to the abdominal cavity, but believes that this particular procedure would be facilitated if the pubes could be brought together and a symphysis restored to allow better closure of the abdominal wall over a reconstructed bladder It was possible passively to compress the pelvis to a degree and it was felt that an osteotomy of the ilium through the greater sciatic notch would be of value in allowing some collapse and reshaping of the pelvic inlet to allow approximating the pubes toward forming a symphysis Besides this particular restoration it would also allow better placing of the hips for walking

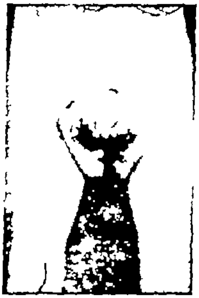

Fig 1 Before operation

"Under a general anesthetic, after the usual surgical preparations, with the child in the prone position the posterior ilium was exposed by anatomic dissection through an incision over the posterior iliac crest and the lateral table exposed subperiosteally The greater sciatic notch was exposed With an osteotome the outer table was osteotomized carrying down to the inner table of the ilium and this was partially osteotomized It was possible then to do an osteoclasis and turn the wing and pubes forward towards the midline This wound was closed in anatomic layers with interrupted deep catgut and black silk to the skin An identical procedure was carried out on the opposite side On completion of the procedure it was possible to bring the pubic bones to within ¾ inch of each other and this resulted in normal placement of the hips An elastoplast retaining dressing was applied and the child immobilized in bed in a pelvic sling A second stage procedure within two or three weeks can be carried out by Dr Shultz and follow-placed in the bladder at the uppermost end where the splint likewise emerged from the now completely constructed bladder Dr Schwartzmann now entered the operation He dissected out each pubic bone and inserted two double coarse silk sutures around each pubic bone pulling them as closely together as possible with the tie Two more triple 000 chromic catgut sutures were then placed in the sphincter muscles and the mucosal flaps sutured together in front of the sphincter with the same material See figures 4 and 5

The abdominal muscles and fascias were then sutured together with No 0 interrupted chromic catgut sutures and the skin edges closed with continuous interlocked silk sutures

Progress was quite satisfactory but after 10 days I thought that the size of the vitallium wire I had used as a splint was too heavy so I replaced it with four coarse strands of silk which would be more comfortable and not nearly so liable to produce cutting or pressure necrosis in the region of the urethra

The next operative procedure was done four weeks after the reconstruction of the bladder On April 1, 1955 I replaced the silk urethral splint with a size 10

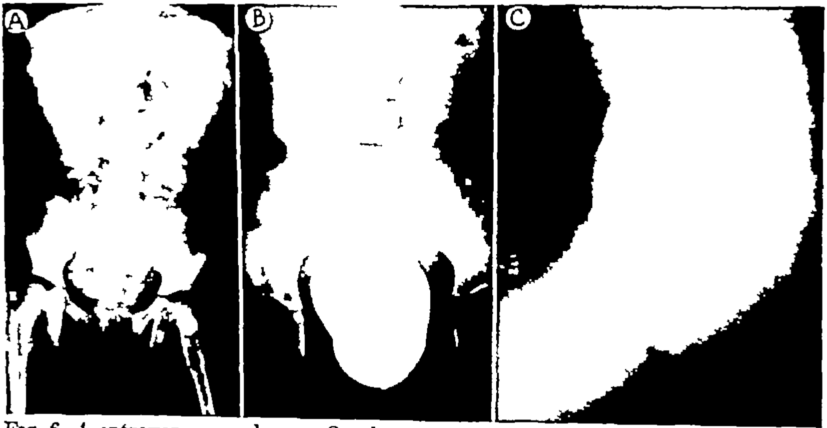

Fig 6 *A*, intravenous pyelogram October 21 1955 seven months, 17 days after surgery *B*, anteroposterior cystogram approximately one year after surgery *C*, lateral cystogram two years after surgery

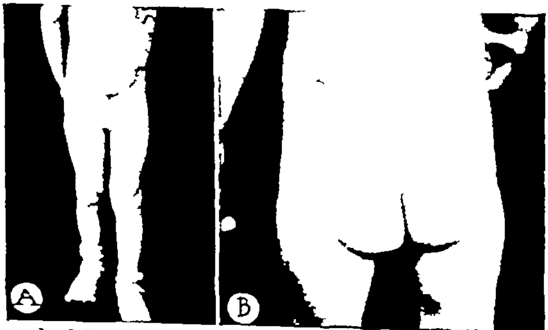

Fig 7 *A* 3 months following surgery *B* location of incisions for bilateral iliostomy

out through the urethra and have sufficient length to tie these ends together outside forming a complete loop insuring against any possibility that they might get out of position or be lost Two triple 000 interrupted chromic catgut sutures were then placed in each arm of the sphincter muscles in such manner as to approximate them in front of the splint thus starting the construction of a sphincter and urethra The bladder edges were then brought together above this with interrupted double 00 chromic catgut sutures A No 16 Foley catheter was

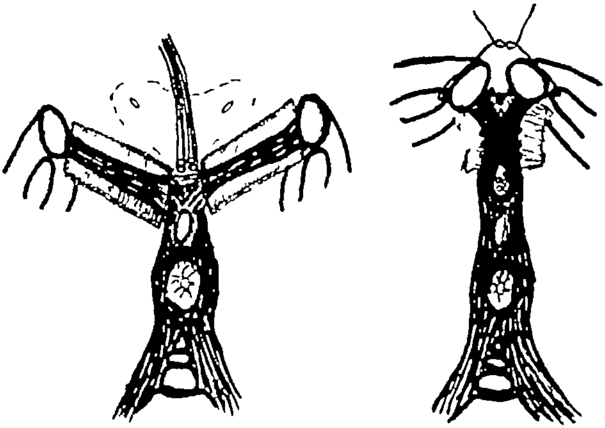

Fig 4 Schematic drawing shows sphincter muscles dissected out, area of mucosa left for urethra where four strands of wire were laid as urethral splint, then sphincter muscles sutured together after close approximation of pubic bones

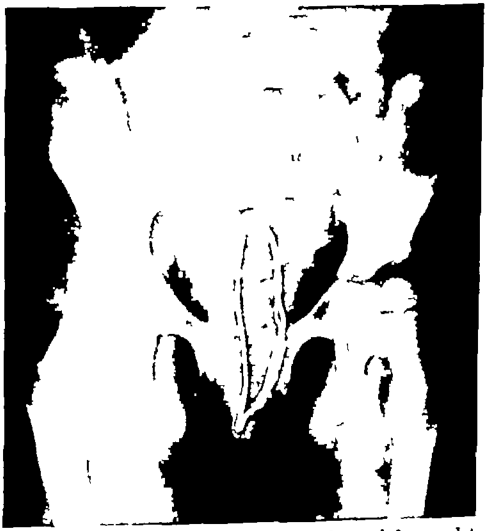

Fig 5 Film taken immediately after operation and used for right tracing in figure 3 In addition to description in legend (fig 3), note vitallium urethral splint

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NEOCYSTOSCOPY AND NEOCYSTOGRAPHY

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Lacking a better term, we have formulated the names "neocystoscopy" and "neocystography" to describe two procedures we have been performing recently.

According to our definition, neocystoscopy is the cystoscopic examination with or without retrograde pyelography of the segment isolated at the time of the operation of ileal bladder substitution. Recent trends in urinary diversion have led to the more frequent use of ileal bladder substitution in which the ureters are implanted into an isolated segment of terminal ileum. We define neocystography as the radiographic examination of a bladder substitute which has been filled with a radiopaque substance.

Having performed a small series of ileal bladder substitutions, we felt the need for more complete postoperative evaluation of the urinary tract and the isolated segment than that afforded by routine methods. Intravenous pyelography was used, but as some kidneys were not functioning adequately prior to surgery it was difficult to determine their status postoperatively. We believed cystoscopy, cystography, and retrograde studies would be valuable for more complete evaluation, and therefore began neocystoscopy, sometimes with retrograde pyelography and, later, with neocystography.

We have been able to carry out neocystoscopy on any patient who has undergone the operation of ileal bladder substitution. It has been employed as early as 24 hours after surgery, as well as more than one year later. It may even be life-saving in establishing the cause of postoperative complications such as anuria, oliguria, volvulus, etc.

Neocystoscopy is not difficult but must be performed several times for the operator to become familiar with the techniques. The patient receives preoperative preparation as for the usual retrograde pyelogram, except that no premedication is administered, and he is placed in either the recumbent or the lithotomy position. Since deep anesthesia is not necessary, we have used 30 mg. nisentil intravenously or intramuscularly for analgesia with good results. General or spinal anesthesia has not been required. Following the preparation and draping of the skin of the abdomen and the skin surrounding the stoma, the patient is placed in slight Fowler's position to allow the waste irrigating fluid to run into the collecting pan of the table. The solution should be as near body temperature as possible to help prevent spasm of the segment while the procedure is in progress, and examination should be done as rapidly as possible for the same reason.

A finger is passed carefully into the isolated loop to aid in determining its course, and the McCarthy panendoscope or Brown-Buerger cystoscope is inserted into the ileal segment. If the patient is not completely relaxed when the

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Read at annual meeting of North Central Section of American Urological Association, Mackinac Island, Mich., August 29–31, 1957.

Foley catheter, removed the suprapubic catheter, removed granulation tissue around suprapubic opening, and closed it with sutures

The suprapubic wound healed by first intention in spite of the fact that the size 10 Foley catheter left indwelling through the urethra did not function perfectly Six weeks after the bladder reconstruction this catheter was removed The patient was incontinent for 36 hours after its removal but then became continent except when agitated or crying, and within a week had very satisfactory control with evidence of increasing bladder capacity

At the time of this presentation, the patient, now five years old, has good control of urination, does not have enuresis and has a bladder capacity of 7 ounces Intravenous pyelograms are normal (fig 6) She does have pyuria, which is resistant to all urinary antiseptics but is improving with bladder irrigations, which her mother gives to her The exterior appearance is shown in figure 7

SUMMARY

A combined approach to the surgical correction of exstrophy of the urinary bladder is herewith submitted I believe that the procedure is a new one

One case is hardly enough to prove the value of any procedure However, the results are so striking that I feel justified in presenting it in hopes that it may help others to work out a technique whereby many more similar cases can have their bladders successfully replaced where nature intended them

I wish to extend my most sincere and grateful appreciation to Dr John R Schwartzmann for his very able contribution

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If retrograde pyelography is to be done, catheters are passed in the usual fashion No one instrument is preferred However more often the panendoscope is used successfully on the left, and the cystoscope with right-angle vision on the right Observation of the orifices will indicate best which scope should be used on which orifice Since the panendoscope is usually passed first our first attempt is through it With the catheters in position pyelograms differential studies and dilatations, as well as collection of urine and institution of renal irrigation or drainage, can be performed (fig 2) We were unsuccessful in passing the catheter up either ureter in one patient despite three attempts even though we could see both ureterointestinal anastomoses well and the orifices were funnel-shaped and wide open In such circumstances, a Foley bulb catheter can be held in position and retrograde pyelograms, at least, can be obtained We do not consider this occasional failure in catheterization a deterrent to the procedure, since we have all had the same maddening experience in the catheterization of normal ureters In most patients we have been able to catheterize both ureters, but in some, just one The left seems to be easier to catheterize than the right, probably because of the direction of the angulation incidental to the anastomosis

After we had performed a few neocystoscopies and noted that the uretero-ileal anastomoses were wide open, we thought we could obtain good retrograde pyelograms without the use of ureteral catheters, but by the process of reflux into the renal pelvis We hoped this would not be restricted to ureters that appeared open and funnel-shaped but would also be applicable to those in which the ureteral stomata were smaller and also hoped we could accomplish filling even in those ureters we were unable to catheterize

For this procedure the patient is placed in the recumbent position and, after preparation and draping of the abdomen a size 22F catheter with a 30 cc Foley bag is passed into the ileal segment It is inserted deep enough into the segment so that the balloon distended with 30 cc sterile water is just down to the abdominal wall The size of the bag in relation to the size of the abdominal wall defect retains the catheter in place and acts as an adequate valve so that there is no leakage on subsequent distention of the segment Following a routine x-ray the

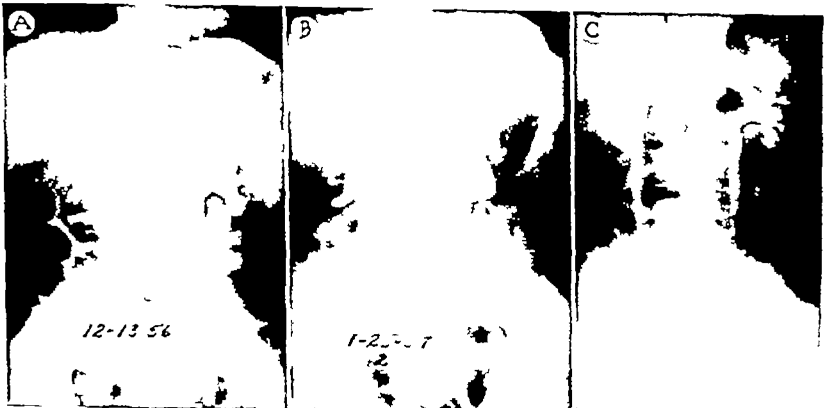

Fig 2

instrument is passed through the abdominal wall, sometimes the wall will "grab" it If the scope is forced at this time, the impression may be that of perforating the ileum Therefore, the instrument must be advanced slowly, preferably under vision, as there are numerous folds in this segment In our small series, we have had no ruptures, although we did experience an anxious moment in one case Nevertheless, it is our opinion that careless manipulation could well lead to a perforated ileum

In those patients in whom the ileal stoma is tight, there should be no difficulty in distending the segment However, in all of our cases, the stomata have been quite large, admitting one finger with ease In these instances, peristaltic contractions of the ileum have caused some leakage of water around the stoma A gauze sponge is wrapped about the sheath of the instrument to prevent ejection of fluid upon the operator We have attempted to compress the stoma around the cystoscope, with only partial success A continuous flow of water is used, and frequently is ejected about the instrument by normal peristalsis, thus washing out mucus plugs and flakes If the segment goes into spasm, since visibility is too poor for evaluation at that moment, manipulation is stopped until relaxation occurs

On first inspection, the ileal segment appears typical of normal ileum, with numerous folds and villi The color is similar to that of normal ileum The panendoscope or cystoscope is manipulated in such a way as to follow the natural curve of the isolated segment as it sweeps deep to the abdominal wall and then laterally across the midline On examining the region of implantation of the right ureter, we have identified the uretero-ileal anastomosis by localized deviations from the normal ileal pattern, such as a funnel-shaped deformity, small radiating folds, or definite small openings similar to "golf hole" orifices (fig 1) If the ureters are not identified, indigo carmine is valuable when the kidney is functioning We also observed that if neocystography is performed first, the orifices are located more easily When proceeding further with the passage of the instrument, it is usually best to depress the eye-piece slightly to locate the left uretero-ileal anastomosis The left anastomosis will appear similar to the right In our cases, the right uretero-ileal orifice usually was closer to the abdominal wall than we anticipated and the left was about one inch from the blind end of the segment We have observed no definite activity of the ureteral orifices, although peristalsis of the ileum itself has been noted

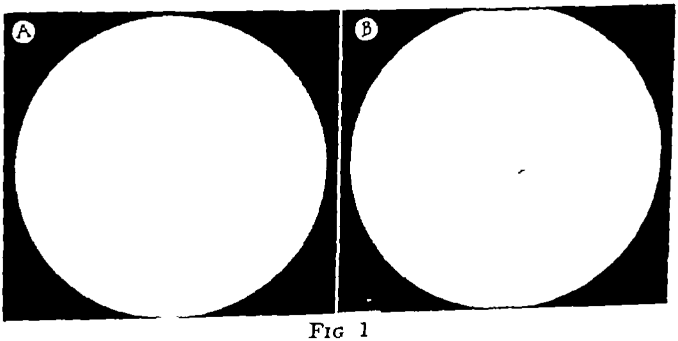

FIG 1

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METABOLIC ALTERATIONS FOLLOWING DIVERSION OF URINE FROM COLON TO ILEAL LOOP

LESTER PERSKY, STANLEY LEVEY, PH.D. AND WILLIAM E. ABBOTT

From the Department of Surgery and the Urological Service, Western Reserve University School of Medicine and the University Hospitals, Cleveland, Ohio

The reportedly high incidence of complications following ureterosigmoidostomy has led many urologists to abandon this type of urinary diversionary procedure in favor of ileal segments or loops.[2] These complications which include hydronephrosis, recurrent pyelonephritis and hyperchloremic acidosis and electrolyte imbalance have been seen despite variations in the technique of the anastomosis and the creation of proximal end colostomies. Besides the hyperchloremic acidosis the electrolyte abnormalities have included a decreased plasma bicarbonate or carbon dioxide combining power, hypokalemia, and an elevated blood urea nitrogen. The etiology of these chemical aberrations has been attributed to reabsorption of chloride from the colon as well as a wasting of fixed base due to associated renal tubular damage or to a combination of both factors. It is evident that the presence of renal damage enhances the likelihood of the development of these electrolyte disturbances.

Ureteroileostomy, either because of the smaller area of absorbing surface or because it is simply a conduit rather than a reservoir, has been attended by little or no body chemical change. The necessity of converting a ureterocolostomy into a ureteroileostomy in a patient who had been previously studied by balance techniques afforded an opportunity to study and compare the differences in the handling of the electrolyte constituents of the blood under both situations in the same patient. Moreover, because of the recent emphasis upon the importance of potassium in the urinary diversions[3] and since potassium balances had been done in the course of the study of this patient and in three others, we felt that our results might help in resolving questions as to the role of potassium in the over-all picture.

METHODS

The patients were maintained on the metabolic division of the University Hospitals of Cleveland during the entire period they were studied. Here it was possible to provide them with both food and parenteral fluids whose content of sodium, potassium, nitrogen and chloride had been determined by analysis

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Read at annual meeting of North Central Section, American Urological Association, Mackinac Island, Mich., August 29-31, 1957.

[1] Ferris, D. O. and Odel, H. M.: Electrolyte pattern of the blood after bilateral ureterosigmoidostomy. J.A.M.A., 142: 634, 1950.

[2] Baker, W. J. and Graf, E. C.: Transplantation of the ureters to an isolated ileostomy. J. Urol., 76: 557, 1956.

[3] Stamey, T. A.: The pathogenesis and implications of the electrolyte imbalance in ureterosigmoidostomy. Surg., Gynec. & Obst., 103: 736, 1956.

ileal segment is filled with radiopaque solution Any one of the solutions may be used, but we use 20 per cent skiodan containing 1 per cent neomycin This dye is allowed to flow in by gravity under 35 mm of water pressure After the segment has been distended, the catheter is clamped and a roentgenogram is made Since we are interested in the cystogram also in these cases, we make oblique as well as the regular AP views Results have been excellent (fig 2, *B*)

Neocystography produces good filling of both kidneys and ureters, when the technique described is followed However, if there is obstruction of a ureteral orifice by tumor, stone, or any other pathological change, it is conceivable that ureters and kidneys would not fill, and it might be impossible to determine the cause Neocystography is somewhat easier than neocystoscopy

We believe that these two procedures make more feasible the complete urinary tract evaluation of the patient who has had ileal bladder substitution, and consider that the ability to perform these two procedures is another factor in favor of the ileal bladder substitution as a method of urinary diversion over many of the other methods

SUMMARY

Neocystoscopy and neocystography are defined, and the procedures are described Neocystography is somewhat easier than neocystoscopy These two procedures make more feasible the complete urinary tract evaluation of the patient who has had ileal bladder substitution

Illustrations accompanying this paper are by courtesy of the Medical Illustration Department, Veterans Administration Hospital, Cincinnati, Ohio

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The reportedly high incidence of complications[1] following ureterosigmoidostomy has led many urologists to abandon this type of urinary diversionary procedure in favor of ileal segments or loops.[2] These complications, which include hydronephrosis, recurrent pyelonephritis and hyperchloremic acidosis and electrolyte imbalance, have been seen despite variations in the technique of the anastomosis and the creation of proximal end colostomies. Besides the hyperchloremic acidosis the electrolyte abnormalities have included a decreased plasma bicarbonate or carbon dioxide combining power, hypokalemia, and an elevated blood urea nitrogen. The etiology of these chemical aberrations has been attributed to reabsorption of chloride from the colon as well as a wasting of fixed base due to associated renal tubular damage, or to a combination of both factors. It is evident that the presence of renal damage enhances the likelihood of the development of these electrolyte disturbances.

Ureteroileostomy, either because of the smaller area of absorbing surface or because it is simply a conduit rather than a reservoir, has been attended by little or no body chemical change. The necessity of converting a ureterocolostomy into a ureteroileostomy in a patient who had been previously studied by balance techniques afforded an opportunity to study and compare the differences in the handling of the electrolyte constituents of the blood, under both situations in the same patient. Moreover, because of the recent emphasis upon the importance of potassium in the urinary diversions,[3] and since potassium balances had been done in the course of the study of this patient and in three others, we felt that our results might help in resolving questions as to the role of potassium in the over-all picture.

METHODS

The patients were maintained on the metabolic division of the University Hospitals of Cleveland during the entire period they were studied. Here it was possible to provide them with both food and parenteral fluids whose content of sodium, potassium, nitrogen and chloride had been determined by analysis

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Read at annual meeting of North Central Section, American Urological Association, Mackinac Island, Mich., August 29–31, 1957.

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ileal segment is filled with radiopaque solution Any one of the solutions may be used, but we use 20 per cent skiodan containing 1 per cent neomycin This dye is allowed to flow in by gravity under 35 mm of water pressure After the segment has been distended, the catheter is clamped and a roentgenogram is made Since we are interested in the cystogram also in these cases, we make oblique as well as the regular AP views Results have been excellent (fig 2, *B*)

Neocystography produces good filling of both kidneys and ureters, when the technique described is followed However, if there is obstruction of a ureteral orifice by tumor, stone, or any other pathological change, it is conceivable that ureters and kidneys would not fill, and it might be impossible to determine the cause Neocystography is somewhat easier than neocystoscopy

We believe that these two procedures make more feasible the complete urinary tract evaluation of the patient who has had ileal bladder substitution, and consider that the ability to perform these two procedures is another factor in favor of the ileal bladder substitution as a method of urinary diversion over many of the other methods

SUMMARY

Neocystoscopy and neocystography are defined, and the procedures are described Neocystography is somewhat easier than neocystoscopy These two procedures make more feasible the complete urinary tract evaluation of the patient who has had ileal bladder substitution

Illustrations accompanying this paper are by courtesy of the Medical Illustration Department, Veterans Administration Hospital, Cincinnati, Ohio

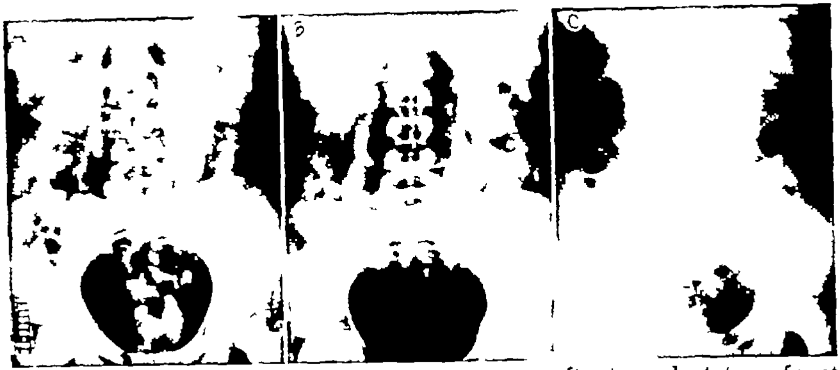

FIG 1 Patient M B *A* excretory urogram, two years after transplantation of ureters to sigmoid, shows bilateral hydronephrosis *B* pyelogram made two years after *A* indicates progressive hydronephrosis *C*, pyelogram six months after ureteroileostomy demonstrates reversal of hydronephrosis

meq/L Intravenous pyelograms revealed a moderate hydronephrosis (fig 1, *A*) Because of evident hyperchloremia, the patient was placed on the metabolic division where balance studies were carried out (fig 2), and ultimately her serum electrolytes were restored to normal values by dietary means in addition to a supplemental intake of potassium citrate and sodium bicarbonate She was discharged with a blood urea nitrogen level of 9 mg per 100 ml

Between 1953 and 1955 the patient had an artificial vagina created from her residual bladder which had been left in situ, and had repeated attempts at closure of a rectovaginal fistula which led to constant perineal soiling The persistence of the small fistula in addition to recurrent pyelonephritis, acidosis and evidence of increasing hydronephrosis (fig 1, *B*) led us ultimately to advise ureteroileal transplants which were carried out in February 1956 Balance studies (fig 2) were done in October 1953 at which time the ureterosigmoidostomy existed and these studies served as a basis for comparison After the conversion operation excretory urograms showed a decrease in the degree of hydronephrosis (fig 1, *C*)

The results of the two metabolic study periods for the patient M.B are depicted in figure 2 The first study period was four years after ureterosigmoidostomy The chloride balance during the time in which the urine was diverted to the colon (ureterocolostomy) showed that on a relatively normal chloride intake of 147 mEq per day, the patient was in a positive chloride balance with a cumulative positive balance of 29 6 mEq for a three day period This became negative on a reduced chloride intake of 66 mEq per day However, throughout this period the plasma chloride level remained high and fell only after three days of the reduced intake from a high of 126 meq/L to 116 meq L, which was still definitely in the hyperchloremic range During this time the CO$_2$ content of the plasma rose from 11 8 to 18 1 meq/L and the pH of the blood increased from 7 25 to 7 34 One year after rerouting of the urine to an ileal loop (ureteroileostomy) balance studies were repeated On approximately the same chloride intake, the patient persisted in negative chloride balance, averaging

The details of the methods used for collecting urine and stool as well as determining the water balance have been described earlier[4] All intake and excreta were analyzed for sodium and potassium using a flamephotometer with a lithium internal standard A similar procedure was used to determine the levels of sodium and potassium in the plasma Nitrogen was determined using the macro Kjeldahl procedure and for chloride, silver titration procedure described by Peters and Van Slyke[5] was employed The urea content of the blood was estimated using the urease procedure of Van Slyke and Cullen[6] The Van Slyke manometric procedure was used to determine the carbon dioxide content of heparinized plasma and the pH of the whole blood was estimated using the procedure described by Craig, Lang, Oberman and Carson,[7] employing a Cambridge pH meter

RESULTS

M B , a 29-year-old white woman, was first seen at University Hospitals in July 1947 at the age of 19 with the chief complaint of total urinary incontinence of two months' duration Previously the patient had been admitted to another institution, and her present difficulty began when in the course of investigating her lack of menses, the urethra was totally divided This was done inadvertently because a congenital absence of the vagina was mistaken for an imperforate hymen On admission here, physical examination revealed a well developed young woman with normal secondary sex characteristics Rectal examination revealed absence of the uterus The vagina was absent and was represented by a short dimple approximately one cm in depth The laboratory data obtained were within the normal range with a blood urea nitrogen concentration of 12 mg per 100 ml Cystoscopy and retrograde pyelograms revealed a completely divided urethra ventrally with an intact bladder and normal upper tracts Three days after admission the urethra was reconstructed over a Foley catheter and a vaginal space created Despite healing of the suture line, the patient continued to be incontinent of urine The artificial vagina was enlarged by the patient by continuous use of plastic molded tampons Between her initial procedure and 1950, she had five subsequent attempts to cure her incontinence including colporrhaphies, plication procedures, and strap operations All of these attempts were unsuccessful She became discouraged and was lost sight of until 1953

During the interim the patient had gone to another hospital where a bilateral ureterosigmoidostomy was carried out Her chief complaint upon readmission was pain in the left flank of 24 hours' duration This was accompanied by chills and fever Since the time of the transplant the patient had had good anal control with no incontinence of urine, but had had recurrent left flank pain She was found to have a blood urea nitrogen of 26 mg per 100 ml and chlorides of 112

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8–10 mEq a day, at both the high and low level of chloride intake It is also of interest to note that on the high intake, 141–150 mEq per day, the chloride level of the plasma never exceeded 113 meq/L, and that the serum chloride concentration did not reach a normal value until the patient had been on the reduced intake for four days The CO_2 content of the plasma ranged between 20 6 and 22 6 meq/L during the entire study and the pH of the blood fluctuated between 7 38 and 7 45

During the first half of the study while the ureterosigmoidostomy was present on an intake of 70–75 mEq of potassium, the patient was in positive balance and retained approximately 20 mEq per day After ureteroileostomy at a somewhat higher intake of 100–108 mEq per day, positive balance was less marked, being close to 10 mEq per day When the potassium intake paralleled that of the first study period (ureterocolostomy), potassium equilibrium was approached The plasma potassium concentration fluctuated between 3 5 and 4 2 mEq per liter

The negative cumulative sodium balance in the eight day period of ureterocolostomy study, on an intake of 110–119 mEq per day, was 130 mEq This included one day in which a sodium deficit of 129 mEq occurred After ureteroileostomy, when the daily sodium intake was somewhat higher at 142 mEq, there was an average daily retention of 18 mEq When the intake was reduced to 48 mEq daily, an average daily deficit of 13 mEq occurred

On an intake of 13 8 gm nitrogen per day during the period when she had a ureterocolostomy, there was a daily positive balance of 6 6 gm When the intake was reduced to 7 2 gm, an average deficit of roughly 2 gm a day occurred With ureteroileostomy on an intake of 12 2–12 9 gm nitrogen daily, the patient was essentially in nitrogen equilibrium

Water balance was similarly followed before and after ureteroileostomy Although insensible loss was merely estimated at roughly one liter per day, it appears as though there was a greater fluid deficit after the ureteroileostomy than prior to it

Metabolic balances of potassium and chloride for three other patients with ureterosigmoidostomy are given in figure 3 Each patient was maintained on both a high and a low chloride intake The figures above each of the metabolic balance charts represent the plasma potassium or chloride levels while the figures below the chloride column represent the carbon dioxide content of the plasma In the case of P B two series of studies were carried out about one month apart This patient had her ureterosigmoid transplant about a month and a half before the first study was undertaken, but because of immediate obstruction at the anastomotic sites, bilateral nephrostomies were done During the first three days of the study the tubes were closed and the urine diverted directly into the colon During the next three days the tubes were opened and the urine drained directly to the outside from the kidneys This whole series was repeated again and the letters O and C below the potassium balance chart represent periods when the nephrostomy tubes were open or closed respectively During the second series of studies the patient received ammonium chloride

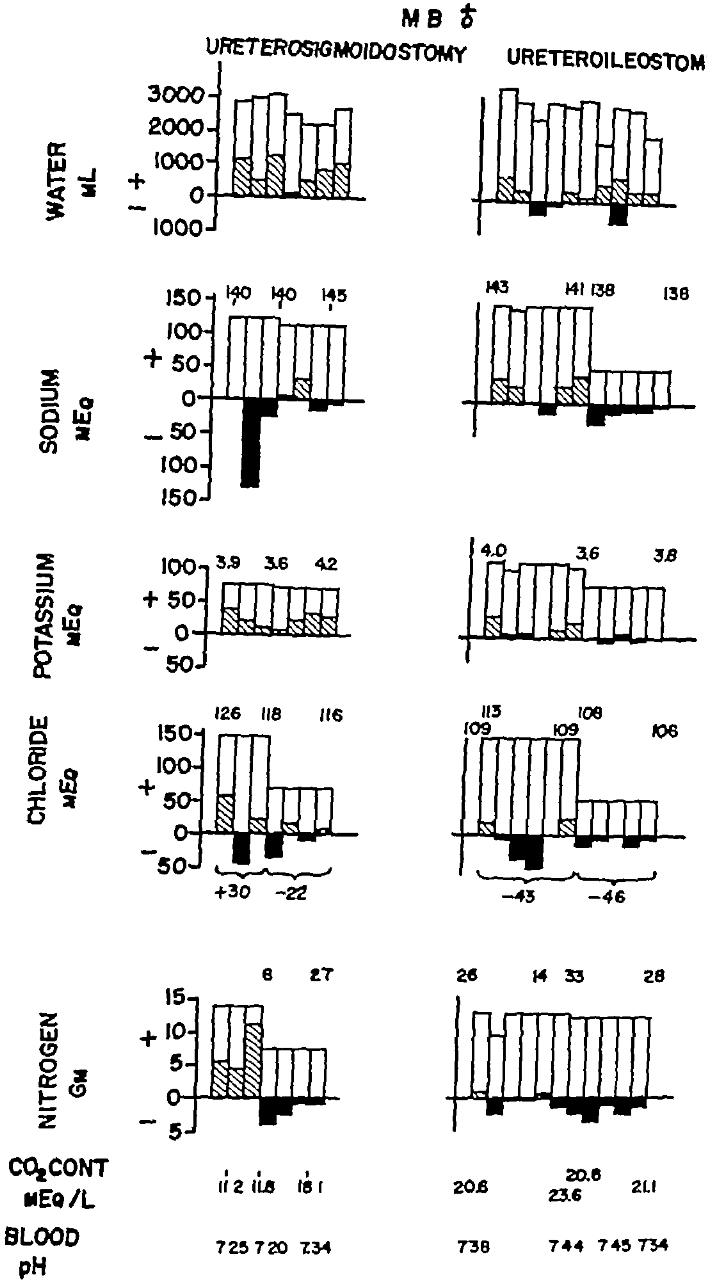

Fig 2 Patient M B Metabolic balance studies four years after ureterosigmoidostomy and a month after ureteroileostomy Daily intake is plotted from zero line upward and output is plotted from top of intake column downward Extension of column below zero line represents negative balance and is illustrated in solid black Positive balance is represented by cross hatched area above zero line Figures above electrolyte columns are plasma values for respective ions Level of blood urea nitrogen is indicated by figures above nitrogen columns

balance of chloride ion. That absorption of this ion can take place from the small bowel has been demonstrated in a variety of ways.[11, 12] That it does not occur here probably reflects the rapid transit time to the exterior.

If one includes the one day of excessive sodium loss, the patient was in negative sodium balance during the first half of her study period. Large sodium losses have been seen in similar patients during periods of acidosis.[4] In addition, laboratory studies[11] have shown restriction of the absorption of sodium from the intestine by polyvalent ions, sulfate, phosphates, etc., a situation which exists in urine. Sodium losses which are accompanied by a loss of water from the constructed cloaca contribute to dehydration, weakness and pyrexia. This was not seen in these patients but did occur in experimental animals where the period of acidosis could be studied for longer periods. The tendency toward greater fluid loss during the second half of the study period possibly reflects less absorption and a more accurate approximation of total renal output.

The role of the potassium ion in the over-all clinical picture of hyperchloremic acidosis is difficult to assay. The occasional case of hypokalemia seen is probably due to a combination of factors. In the recent literature[2] it is suggested that potassium deficiency is one of the prime causes for the weakness, lethargy, anorexia and renal insufficiency seen secondary to ureterosigmoidostomy. Although there is much evidence to adduce renal tubular vacuolar lesions to potassium loss,[13, 14] on the basis of our studies which were perhaps of too short a duration, of patients with ureterosigmoidostomy, we did not demonstrate any excessive potassium loss. On the other hand, in a series of animals with vesicosigmoidostomy[15] large potassium losses occurred concomitant with large chloride deficits. This loss was greatly increased during periods of dehydration. In these animal studies the acidosis was quite severe with blood pH in the vicinity of 7.15.

As Lapides has demonstrated,[16] the presence of renal damage enhances the likelihood of acidosis and they feel that perhaps it is a prerequisite for its development. If one were to suggest that potassium deficiency is the prime difficulty with ureterosigmoidostomy it would appear to us to be corroboratory evidence for the thesis of underlying renal damage since the anatomical lesions of potassium depletion (vacuolization) have been demonstrated. On the basis of our studies which fail to show potassium deficits we cannot support a thesis which attributes hyperchloremic acidosis to a potassium deficit.

Still to be considered are those patients with ureterosigmoidostomy who

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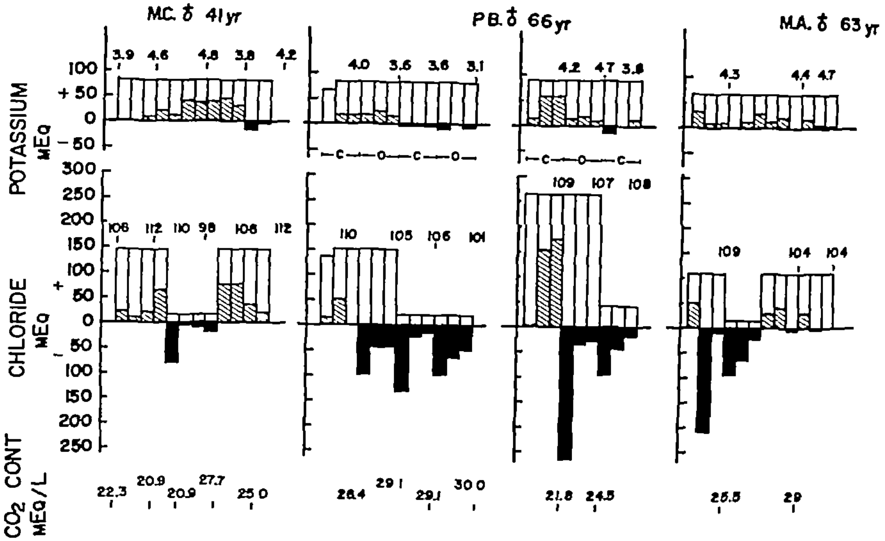

Fig 3 Chloride and potassium balances for three patients following ureterosigmoidostomy, each maintained on two different chloride intakes Graphing is similar in plan to figure 2 Letters C and O under potassium balances for patient P B indicate time when nephrostomy tubes were open or closed

tablets for the first six days This accounted for the high chloride intake The nephrostomy tubes were closed for the first three and the last two days of this study For the balance studies of all four patients it appears that there is no evidence of potassium wasting In these patients, the fluctuation of potassium did not appear to be dependent upon the chloride balance since one must consider the total anion and cation intake and exchange

DISCUSSION

These metabolic balances show that on relatively normal intake of chloride there was a marked difference in the handling of this anion when contrasting ureterosigmoidostomy with ureteroileostomy In patient M B, when urine entered the colon, she showed a retention of chloride seen in similar studies on other patients[8] With the use of an ileal shunt as a urinary conduit, no retention of chloride was encountered The absorption of chloride from the intestine has been demonstrated to proceed at a greater rate than the absorption of sodium,[9] and this is accompanied by an exchange for bicarbonate[10] These exchanges make the frequent occurrence of acidosis in patients with urinary diversion to the large bowel readily understandable The infrequent development of hyperchloremic acidosis with the use of the ileal pouch is readily apparent when as a contrasting factor there is the absence of the acidifying effect of a positive

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THE ABSORPTION OF SODIUM FROM THE HUMAN URINARY BLADDER

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For the past several years numerous investigators have reported the absorption of a variety of drugs and toxic substances from the urinary bladder[1] [2] In general, these studies have been conducted in subjects with severe bladder disease A recent study from this laboratory showed that sodium and other electrolytes were absorbed from the bladder of dogs in significant amounts[3] Furthermore, the rate of transfer was shown to be a function of the pH of the bladder contents resulting in a maximum transfer at low pH values

The present study was initiated to establish whether or not sodium is absorbed from the human bladder and, if so, to examine its importance in the electrolyte imbalance that occasionally results after the relief of lower urinary tract obstruction

METHODS AND MATERIALS

Twenty studies were performed in as many patients, who were selected because of a poor prognosis with regard to their primary disease

Three groups of subjects were studied 1) those with chronically infected bladders established by history, urinalysis and cystoscopy (in most of these subjects there was evidence of prostatic obstruction), 2) paraplegics with chronically infected bladders, and 3) patients with normal urinary bladders In the latter group the pH of the urine was altered by administration of either sodium citrate or ammonium chloride several days prior to the study In six subjects a low sodium diet and cortisone were employed to minimize the amount of sodium excreted in the urine during the period of the experiment All subjects went without food and water 12 hours prior to the study, thus minimizing urinary volumes during the study period Foley catheters were inserted into the bladder 12 hours before the study Immediately preceding each experiment a 30-minute collection of urine was obtained for control values of sodium and potassium, and urinary excretory volume The bladder was then drained and washed several times with sterile, distilled water One hundred to two hundred microcuries of sodium 24 were then instilled into the bladder, followed by two washes of sterile, distilled water to assure complete delivery of the isotope Concentrations of the saline infusate ranged from 5 meq/L to 155 meq/L Blood samples were obtained from the antecubital vein every 10 minutes for the next hour and 30 minutes for the following two hours At the end of three hours the fluid in the bladder was removed and the bladder was washed out twice with sterile, distilled water Plasma and urine samples were analyzed for radioactivity in a RC

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have never demonstrated electrolyte abnormalities Since we have not done balance studies on patients of this type, we can only infer as to possible differences between these two groups Perhaps the numerous factors which influence the blood electrolyte concentrations in these patients and the amount of chloride vs sodium or potassium intake (area of absorbing surface, transit time, fluid intake, dietary habits etc) account for the normal values encountered In addition, the anatomical setup may be such that renal damage of varying degree does not occur In those patients where hyperchloremic acidosis occurs, the metabolic balance studies presented show that ureteroileostomy will cause reversal of the acidosis and will prevent recurrent infection

SUMMARY

A series of patients with ureterosigmoidostomy have been studied in terms of sodium, potassium, nitrogen, and chloride balances In one patient the conversion to ureteroileostomy afforded an opportunity to compare metabolic balances under both situations No evidence was found to support a theory of potassium wasting The balances following ureteroileostomy showed a reversal of the pattern previously noted for diversion into the large bowel

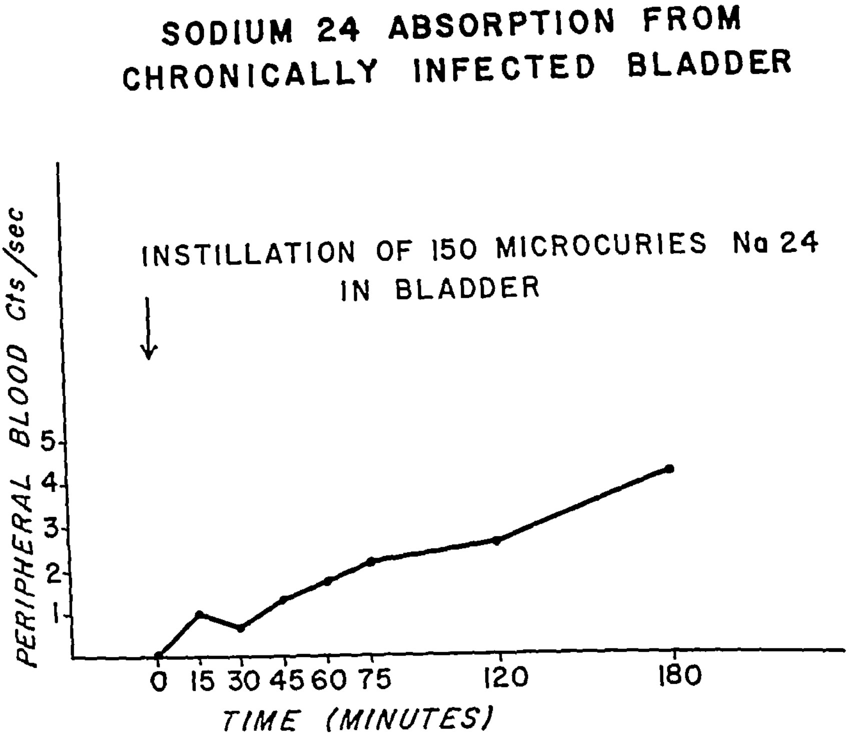

Fig 1

in an 85 pound individual with bilateral hip amputations and both acute and chronic cystitis

DISCUSSION

These findings indicate that sodium is not absorbed through the intact bladder of man This is exactly the opposite to the situation as reported in dogs by Hlad, Nelson and Holmes[3]

This experiment was originally designed to determine whether significant amounts of sodium pooled within the chronically inflamed and obstructed bladder might be absorbed, and thus account for the tremendous sodium diuresis that occasionally[4] occurs following the relief of chronic and acute urinary obstruction The present findings suggest that the absorption of sodium from the urinary bladder plays little or no part in such a sodium diuresis

SUMMARY

In man (contrary to the situation in the dog) sodium absorption from the bladder is minimal and is not altered by changing the pH of the urine or with inflammation of the bladder wall

Bladder absorption of sodium is not an important etiologic factor in the production of sodium and water imbalance following the relief of lower urinary tract obstruction

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TABLE 1. *Sodium 24 absorption from bladder*

	Diagnosis	Bladder Condition	Experimental Procedure	Urine pH	Recovery in Plasma at 3 hrs	Recovery in Bladder at 3 hrs
					%	%
J. E.	Varicose veins	Normal	Dehydration—ammonium chloride	4.5	<0.1	95.6
A. H.	Skin cancer	Normal	Dehydration—sodium citrate	7.8	<0.1	98.7
C. W.	Prostatic hypertrophy	Acute infection	Dehydration	5	<0.1	98.5
L. I.	Cystitis	Chronic infection	Dehydration	—	<0.1	96.0
E. B.	Prostatic hypertrophy	Acute & chronic	Dehydration	—	<0.1	95.6
R. M.	Carcinoma of stomach	Chronic infection	Low salt diet—cortisone	Acid	<0.1	72.4*
J. N.	Prostatitis	Acute & chronic	Low salt diet—cortisone	—	<0.1	98.8
J. R.	Quadriplegia	Acute & chronic	Dehydration	—	<0.1	78.8*
C. M.	Multiple sclerosis	Acute infection	Low salt diet—cortisone	7.4	<0.1	95.8
R. S.	Carcinoma of rectum	Chronic infection	Low salt diet—cortisone	5	<0.1	96.8
R. K.	Quadriplegia	Acute & chronic	Low salt diet—cortisone	5	<0.1	98.5
W. R.	Paraplegic	Acute & chronic	Low salt diet—cortisone	5.4	<0.8	95.4
W. L.	Prostatic hypertrophy	Acute & chronic	Dehydration	5.9	<0.1	95.0
W. G.	Prostatic hypertrophy	Acute infection	Dehydration	Acid	<0.1	98.2
O. G.	Prostatic hypertrophy	Acute infection	Dehydration	Acid	<0.1	96.8
V. P.	Prostatitis	Normal	Dehydration—sodium citrate	7.7	<0.1	96.7
C. N.	Prostatic hypertrophy	Normal	Dehydration	—	<0.1	97
K.	Prostatic hypertrophy	Normal	Dehydration	—	<0.1	94
P.	Prostatic hypertrophy	Normal	Dehydration	—	<0.1	98
F.	Prostatic hypertrophy	Normal	Dehydration	—	<0.1	99

* Some urine was lost during end of procedure.

One hundred to two hundred microcuries of Na^{90} were instilled into the bladder.

scientific scintillation well counter. Initial and final pH values were determined on plasma and urine with a Beckman model G pH meter. Plasma and urine sodium were determined with a Beckman flame photometer.

RESULTS

A summary of the results of these experiments is shown in table 1, and a typical plasma recovery pattern shown in figure 1. It will be noted that with two exceptions—when some urine was accidentally lost during the washout—95 per cent or more of the instilled Na^{24} was recovered in the bladder contents. Neither alteration of pH, nor of the sodium concentration of the instillate from 5–155 meq/L significantly affected the absorption of sodium from the bladder. Similarly, the nature of the accompanying cystitis did not alter the absorptive capacity. In only one patient (W. R.) was there significant absorption, and this

Radiation therapy of bladder cancer by supervoltage equipment has been reported by Buschke to give encouraging results Stapleton, of the Royal Cancer Hospital in London, reported pleasing short term results in advanced bladder cancer following the use of two million volt rotation x-ray therapy He reported a lack of radiation symptoms and absence of severe skin and rectal reactions

We believe that the selection of the type of treatment for each case should depend on the general condition of the patient, the gross appearance of the tumor (papillary or infiltrating), microscopic appearance, its extent and location within the bladder (anterior wall, lateral wall or trigone), whether there are single or multiple tumors, obstruction of ureteral or urethral orifices, involvement of the bladder sphincter, upper urinary tract function, presence of infected kidneys, previous treatment, presence of disease outside of the bladder by local extension, lymph node metastases or distant metastases

We propose the following clinical classification which is based on the gross appearance of the tumor and its extent The specific treatment which is outlined is discussed on the basis of this clinical classification

CLINICAL CLASSIFICATION

Clinical stage 0 Single or multiple *papillary* tumors which are histologically *benign*

Clinical stage 1 Single or multiple *papillary* tumors which are histologically *malignant*

Clinical stage 2 Single or multiple *infiltrating* tumors *without extension* through the bladder wall

Clinical stage 3 *Infiltrating* tumors *penetrating* through the bladder wall to perivesical tissue and with or without regional lymph node metastasis

Clinical stage 4 *Infiltrating* tumor *with* distant *metastases*

SPECIFIC TREATMENT

For clinical stage 0 (benign papillary) These are single or multiple papillary tumors which are histologically well differentiated They usually respond very poorly to any type of external radiation therapy whether it is conventional x-ray treatment or supervoltage therapy The total dose of internal irradiation required to eradicate these tumors often approaches the effect of an actual cautery Therefore, the subsequent scarring and post-radiation necrosis do not warrant its use since these tumors are actually benign for long periods of time The "recurrences" may be new tumors in other portions of the bladder mucosa Therefore, there is no assurance that caustic internal or interstitial irradiation of the initial tumor will prevent recurrence elsewhere in the bladder mucosa Also, the "prophylactic use" of the cobalt bomb has not always prevented the development of new bladder tumors We prefer to use cystoscopic fulguration followed by cystoscopic inspection at intervals of two to three months A biopsy of any suspicious area of recurrence is made in order to rule out actual malignant change in the base of the tumor Fulguration through the cystoscope is continued unless the tumor shows histological evidence of malignancy

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TREATMENT OF BLADDER AND PROSTATIC CANCER BY COMBINED INTERSTITIAL ISOTOPE RADIATION AND THE COBALT BOMB

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BLADDER CARCINOMA

The cumulative survival rate by years for hundreds of treated patients compared with a large series of untreated patients reveals that the treatment of bladder cancer prolongs life appreciably and affords a marked degree of palliation

The histologic pattern of a large number of urinary bladder tumors shows a transitional cell carcinoma This type of tumor is highly *radiosensitive* Therefore it might be expected that external irradiation would cause these tumors to be *radiocurable* However, urologists and radiation therapists have found that the sterilization of bladder cancer is rarely accomplished following x-ray therapy with conventional 200–250 KV machines Radiocurability probably depends on a sufficient penetration of the radiation beam, the accurate direction of the beam beyond all margins of the tumor, an adequate cancerocidal tumor dose, the general condition of the patient, the control of infection in the upper urinary tract as well as the radiosensitivity of the tumor As a *palliative* measure this type of x-ray treatment has occasionally been successful, but generally it has given poor results When heavy doses of x-ray therapy were administered by 200 KV machines, many patients subsequently developed secondary contraction of the bladder This, together with the residual disease, produced a lasting pain Another distressing complication sometimes occurring in patients who had been "cured" by conventional x-ray therapy was severe and uncontrollable hematuria due to telangiectasia and severe atrophy of the bladder mucosa

Other methods of treatment have therefore been given preference These procedures include a) *cystoscopic fulguration* with or without implantation of radon seeds or internal radiation therapy by a radium or cobalt bead in a special indwelling catheter, b) *open bladder surgery* with resection and fulguration of the tumor base with or without the implantation of radon seeds, radium needles, radioisotope injections or implantation of cobalt sources in nylon threads, c) *segmental resection* with or without interstitial irradiation, d) *total cystectomy* with implantation of the ureters into the bowel or skin

Since we have observed the limitations of total cystectomy in a series of 80 patients, we decided to explore the value of *interstitial irradiation* by radioactive colloidal chromic phosphate injection through the open bladder plus *external irradiation* by supervoltage therapy delivered by the cobalt bomb

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Read at annual meeting of Western Section of American Urological Association Seattle Wash , May 27–30 1957

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Radiation therapy of bladder cancer by supervoltage equipment has been reported by Buschke to give encouraging results Stapleton of the Royal Cancer Hospital in London reported pleasing short term results in advanced bladder cancer following the use of two million volt rotation x-ray therapy He reported a lack of radiation symptoms and absence of severe skin and rectal reactions

We believe that the selection of the type of treatment for each case should depend on the general condition of the patient the gross appearance of the tumor (papillary or infiltrating) microscopic appearance its extent and location within the bladder (anterior wall lateral wall or trigone), whether there are single or multiple tumors obstruction of ureteral or urethral orifices involvement of the bladder sphincter upper urinary tract function presence of infected kidneys, previous treatment presence of disease outside of the bladder by local extension lymph node metastases or distant metastases

We propose the following clinical classification which is based on the gross appearance of the tumor and its extent The specific treatment which is outlined is discussed on the basis of this clinical classification

CLINICAL CLASSIFICATION

Clinical stage 0 Single or multiple *papillary* tumors which are histologically *benign*

Clinical stage 1 Single or multiple *papillary* tumors which are histologically *malignant*

Clinical stage 2 Single or multiple *infiltrating* tumors *without extension* through the bladder wall

Clinical stage 3 *Infiltrating* tumors *penetrating* through the bladder wall to perivesical tissue and with or without regional lymph node metastasis

Clinical stage 4 *Infiltrating* tumor *with* distant *metastases*

SPECIFIC TREATMENT

For clinical stage 0 (benign papillary) These are single or multiple papillary tumors which are histologically well differentiated They usually respond very poorly to any type of external radiation therapy whether it is conventional x-ray treatment or supervoltage therapy The total dose of internal irradiation required to eradicate these tumors often approaches the effect of an actual cautery Therefore the subsequent scarring and post-radiation necrosis do not warrant its use since these tumors are actually benign for long periods of time The recurrences may be new tumors in other portions of the bladder mucosa Therefore there is no assurance that caustic internal or interstitial irradiation of the initial tumor will prevent recurrence elsewhere in the bladder mucosa Also, the prophylactic use of the cobalt bomb has not always prevented the development of new bladder tumors We prefer to use cystoscopic fulguration followed by cystoscopic inspection at intervals of two to three months A biopsy of any suspicious area of recurrence is made in order to rule out actual malignant change in the base of the tumor Fulguration through the cystoscope is continued unless the tumor shows histological evidence of malignancy

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TREATMENT OF BLADDER AND PROSTATIC CANCER BY COMBINED INTERSTITIAL ISOTOPE RADIATION AND THE COBALT BOMB

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BLADDER CARCINOMA

The cumulative survival rate by years for hundreds of treated patients compared with a large series of untreated patients reveals that the treatment of bladder cancer prolongs life appreciably and affords a marked degree of palliation

The histologic pattern of a large number of urinary bladder tumors shows a transitional cell carcinoma This type of tumor is highly *radiosensitive* Therefore it might be expected that external irradiation would cause these tumors to be *radiocurable* However, urologists and radiation therapists have found that the sterilization of bladder cancer is rarely accomplished following x-ray therapy with conventional 200–250 KV machines Radiocurability probably depends on a sufficient penetration of the radiation beam, the accurate direction of the beam beyond all margins of the tumor, an adequate cancerocidal tumor dose, the general condition of the patient, the control of infection in the upper urinary tract as well as the radiosensitivity of the tumor As a *palliative* measure this type of x-ray treatment has occasionally been successful, but generally it has given poor results When heavy doses of x-ray therapy were administered by 200 KV machines, many patients subsequently developed secondary contraction of the bladder This, together with the residual disease, produced a lasting pain Another distressing complication sometimes occurring in patients who had been "cured" by conventional x-ray therapy was severe and uncontrollable hematuria due to telangiectasia and severe atrophy of the bladder mucosa

Other methods of treatment have therefore been given preference These procedures include a) *cystoscopic fulguration* with or without implantation of radon seeds or internal radiation therapy by a radium or cobalt bead in a special indwelling catheter, b) *open bladder surgery* with resection and fulguration of the tumor base with or without the implantation of radon seeds, radium needles, radioisotope injections or implantation of cobalt sources in nylon threads, c) *segmental resection* with or without interstitial irradiation, d) *total cystectomy* with implantation of the ureters into the bowel or skin

Since we have observed the limitations of total cystectomy in a series of 80 patients, we decided to explore the value of *interstitial irradiation* by radioactive colloidal chromic phosphate injection through the open bladder plus *external irradiation* by supervoltage therapy delivered by the cobalt bomb

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This work was supported by a grant from the U S Atomic Energy Commission contract No AT (OH 3) 57 considered suitable for cystectomy This includes 1) those patients with trigone involvement who cannot be treated by interstitial therapy because it would destroy the ureteral orifices, 2) those patients with infiltration of the outlet of the bladder requiring local destruction of the sphincters, 3) multiple infiltrating tumors of the bladder, 4) recurrent spreading low-grade malignant tumors involving large areas of the bladder, and 5) superficial tumors becoming highly malignant or infiltrating and penetrating in type

For clinical stage 4 (distant metastases) Palliative cobalt therapy is employed to reduce hematuria and attempt to cause as much regression of the tumor as is possible for palliation and prolongation of life Smaller total tumor doses of cobalt radiation therapy are prescribed for these patients since only palliation is possible

SUPPORTIVE TREATMENT

The general condition of the patient must be evaluated and appropriate supportive measures prescribed to control hematuria and replace loss of blood by transfusions If infection is present in the bladder or the upper urinary tract, antibiotics are administered If there is a nonfunctioning infected kidney it should be removed surgically when the infection cannot be controlled by medical means If the function of the upper urinary tract is poor and if the edema of radiation therapy threatens to obstruct the proper drainage of the kidneys, it may be necessary to perform a nephrostomy or transplant the ureters to the skin

RADIATION THERAPY

1) *Internal radiation* After the bladder has been opened and the need for interstitial radiation is apparent, we now usually employ radioactive colloidal chromic phosphate by the multiple long needle technique, as we have previously described for the palliative treatment of advanced prostatic cancer We have sub-

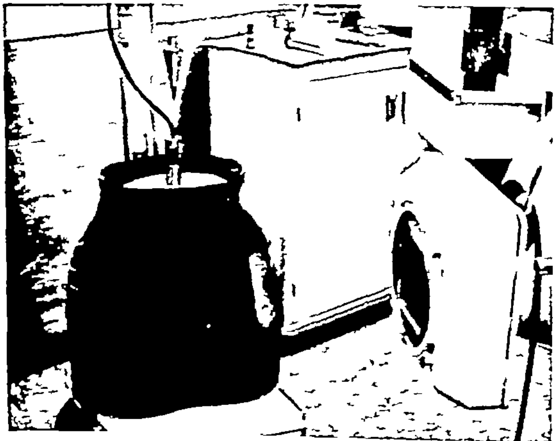


FIG 1 Plastic phantom of patient with carcinoma of bladder Phantom is filled with special bolus material having same specific density as tissue Radocon instrument is placed at tumor site and it directly measures dose of radiation from cobalt beam

For clinical stage 1 (malignant papillary) a) *For the single malignant papillary tumor,* cystoscopic fulguration with implantation of radon may be attempted if there is no definite evidence of infiltration This type of tumor must be watched carefully for the patient may subsequently show evidence of local recurrence with or without infiltration of the bladder wall, or there may be multiple tumors developing in other areas of the bladder mucosa

b) *For recurrent single papillary* malignant tumors *or for multiple papillary* malignant tumors we perform open bladder surgery If there is no penetration of the bladder wall, a segmental excision is performed when the tumor is anterior or lateral in location and when a sufficient amount of functioning bladder will remain If the tumors are too extensive for segmental resection or if the trigone or outlet is involved, we prefer fulguration and interstitial implantation of radioactive colloidal chromic phosphate This is followed by a full course of external rotation cobalt therapy if there is subsequent recurrence of tumor

For clinical stage 2 (infiltrating) Segmental resection is done when there is a single infiltrating tumor which on open bladder inspection and palpation is found to be completely resectable No interstitial irradiation is employed because theoretically all of the tumor has been removed surgically Only when subsequent microscopic examination reveals that an inadequate amount of surrounding normal mucosa has been removed do we employ postoperative cobalt bomb therapy Also, if subsequent examination reveals evidence of local recurrence we prescribe cobalt bomb treatment If the tumor is nonresectable we remove the bulk of it by electrosurgery and fulgurate its base Then we inject the isotope or radon seeds The cobalt bomb is used only is there is residual disease after three months as determined by biopsy When cystoscopy reveals multiple infiltrating tumors, we fulgurate each tumor to its base after removing the bulk of it by electrosurgery Radon seeds or the isotopes are injected at the tumor base, and cobalt bomb therapy is used after three months if the inspection biopsy is positive

We have also treated a few of these patients by external cobalt bomb therapy without open surgery, and some of them have done well This has usually been prescribed when there was some medical contraindication to open surgery (coronary disease)

For clinical stage 3 (infiltrating, penetrating or requiring total cystectomy) When open surgery reveals that the neoplasm is infiltrating and extending through the bladder wall into the perivesical fat or into the regional lymph nodes, we remove the bulk of the tumor by electrosurgery and fulgurate its base We also remove a lymph node for biopsy if it appears to be involved by metastatic disease, and inspect the liver for evidence of metastasis If the liver is not grossly involved we record the extent of the lymph node metastases and then give these patients intensive postoperative cobalt bomb therapy We do not use interstitial irradiation for this stage of tumor If there is local recurrence after cobalt bomb treatment, a "second look" operation is performed and interstitial isotope injection is carried out

We now prefer to use cobalt bomb therapy for all patients who were previously

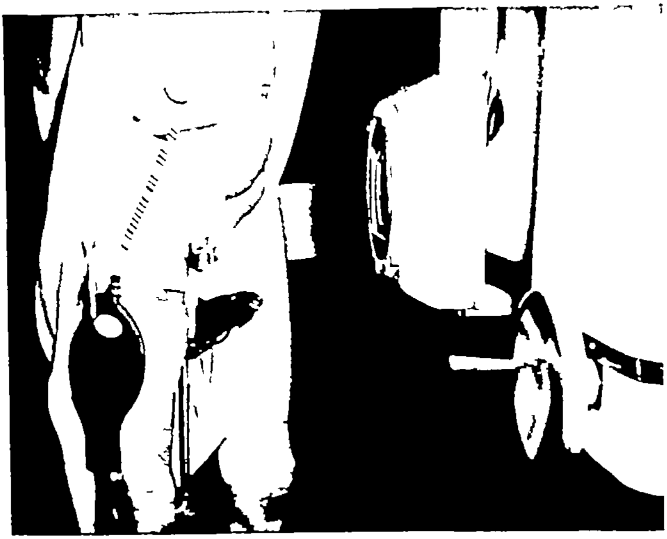


FIG 3 Patient with carcinoma of bladder in vertical position on rotating chair during cobalt bomb therapy

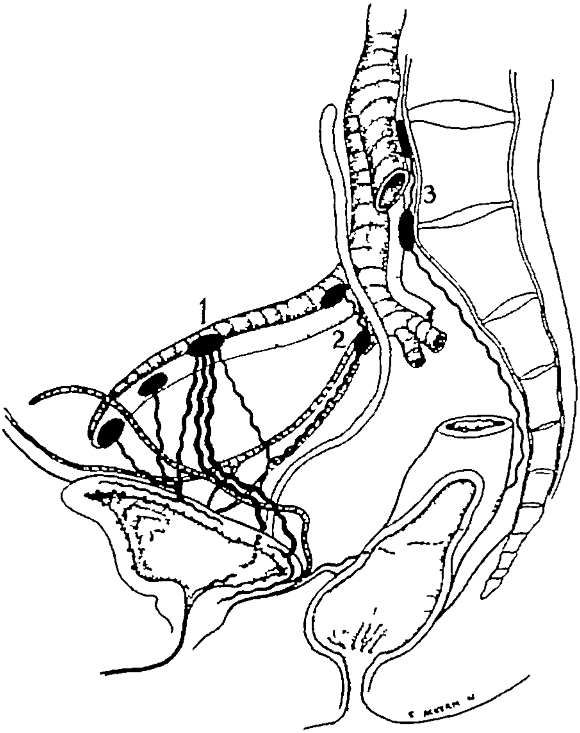
vantages over conventional x-ray therapy as delivered by 200 to 250 KV machines Cobalt-60 has a higher energy which is equivalent to about three million volt x-rays This higher energy permits better protection of the skin while we are able to deliver a much higher tumor dose The depth dose pattern in the tumor area is superior There is less bone damage because there is not as much backscatter Also, dosage measurements are simpler because there is less backscatter Sharper collimation is possible with the cobalt beam, and it is a better beam for rotation therapy since the optimum energy for rotation is about one million electron volts The average cobalt beam is 1 25 million electron volts There are fewer maintenance problems and there is much less radiation sickness

Rotation cobalt therapy has certain advantages over stationary cobalt therapy The rotation therapy permits a higher total tumor dose with less skin damage and it simulates multiple port techniques The distribution of the radiation is improved, and there is less chance of overlap of multiple fields Rotation therapy will produce less damage to the normal tissues since the maximum dose is at the tumor site and the dose falls off away from the tumor site With the stationary technique the maximum dose is under the skin and falls off as the tumor site is approached Less time is necessary for setting up the patient as compared to the multiple port technique

There are certain physical advantages of the phantom dose (fig 1) measurements which we use with cobalt-60 radiation as compared to calculations and tables which are used for determining tumor dosage as given by conventional x-ray therapy The phantom measurement provides a quick and direct means of obtaining the actual dosage value both in the tumor volume and outside the tumor volume in any plane It takes into consideration minor variations in body stituted this isotope injection treatment for radon seeds which we previously used for the same purpose The isotope which is prepared from radioactive phosphorus (P^{32}) has a physical half-life of 14 3 days and is composed entirely of beta radiation which has a maximum penetration of 8 mm of tissue It delivers a total dose of 885,000 roentgen equivalents physical to 1 gm or cc tissue containing 1 millicurie of the isotope completely disintegrating We feel that this isotope will probably prevent some of the complications which followed the use of radon seed implantation since we have eliminated the more penetrating gamma radiation present in the radon seeds When radon seeds are used we prefer the gold seeds which contain about 1 to 1 5 millicuries of radon per seed These are implanted in a radial manner at a distance of about 1 cm apart

When we use the long needles for the injection of the isotope they are placed about ½ cm apart and each needle is injected with 3 millicuries of the isotope The chromic phosphate preparation contains 2 millicuries of P^{32} per cc fluid The operator has adequate radiation protection by the plastic shield over the special syringe which contains a disposable cartridge

2) *External radiation* We have found that cobalt-60 therapy has certain ad



An [illegible] sketch of the lymphatics of the bladder drained mainly by 1 the external iliac nodes but also by 2 hypogastric and 3 common iliac nodes.

Fig 2 Schematic drawing of lymphatics of bladder

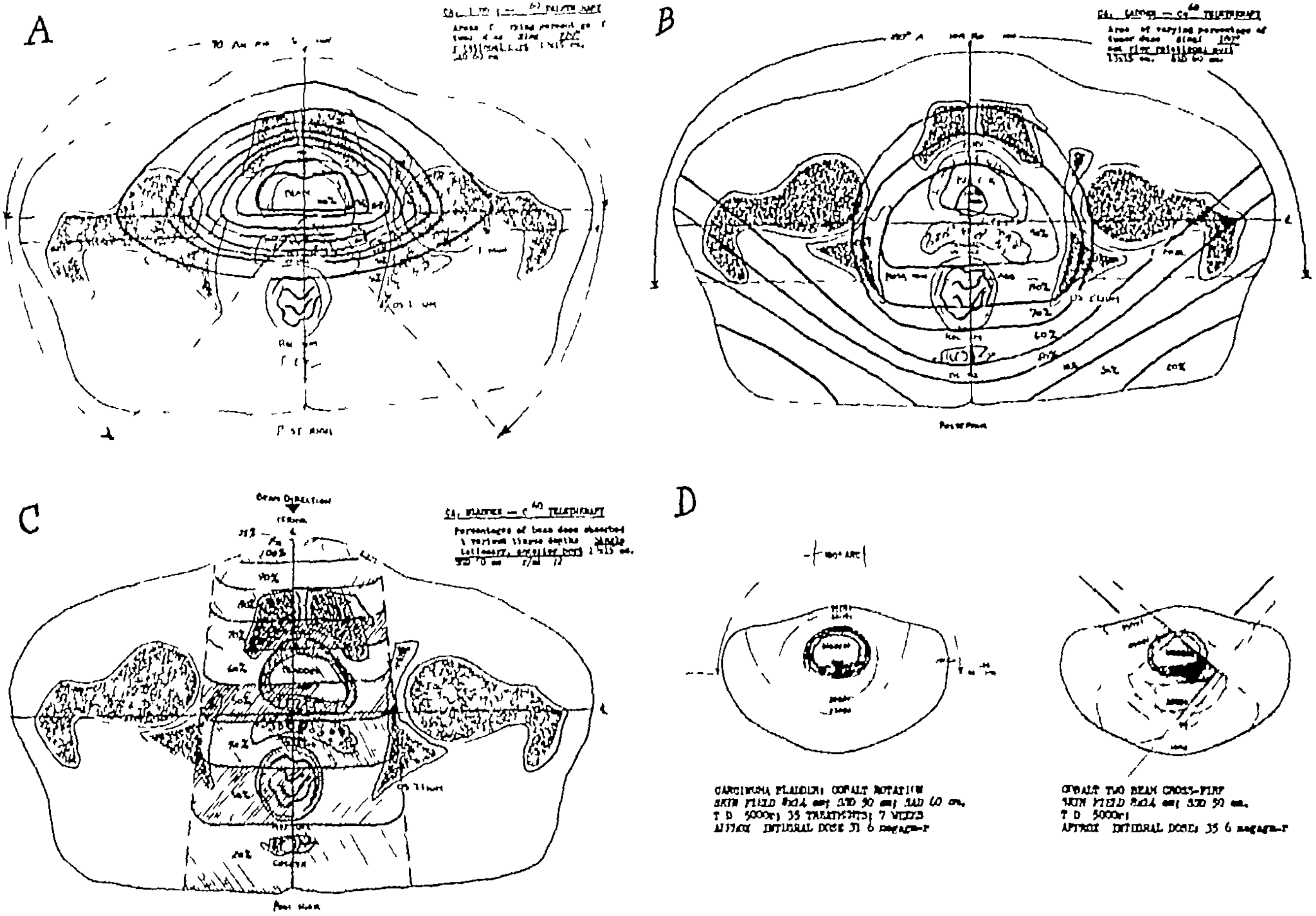

A
B
C
Beam Direction
D
CARCINOMA BLADDER: COBALT ROTATION
SKIN FIELD 8x14 cm; SSD 50 cm; SAD 60 cm.
T D 5000r; 35 TREATMENTS; 7 WEEKS
APPROX INTEGRAL DOSE 31 6 megagm-r
COBALT TWO BEAM CROSS-FIRE
SKIN FIELD 8x14 cm; SSD 50 cm.
T D 5000r;
APPROX INTEGRAL DOSE: 35 6 megagm-r

FIG 6 *A*, 270° anterior rotation pattern for carcinoma of bladder *B*, 180° anterior rotation pattern for carcinoma of bladder *C*, stationary anterior beam for carcinoma of bladder, showing isodose pattern Bladder is in 60 per cent zone and rectum is in 30 per cent zone *D*, cobalt bomb therapy for carcinoma of bladder by two beam crossfire, showing overlap of two fields, as compared to isodose

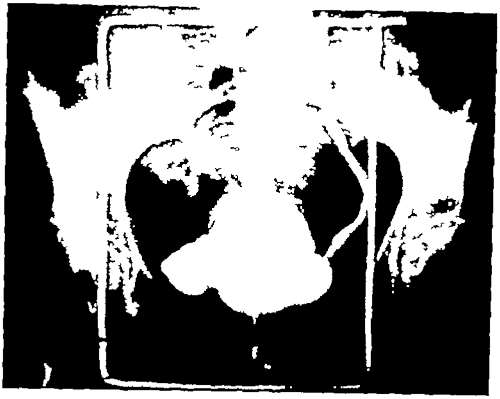


FIG 4 Anteroposterior cystogram with wire marker on patient's skin delineating area covered by the cobalt beam

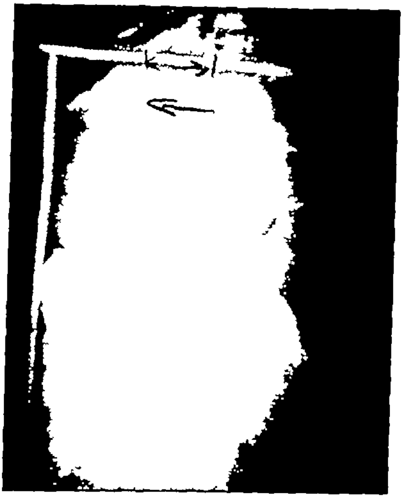
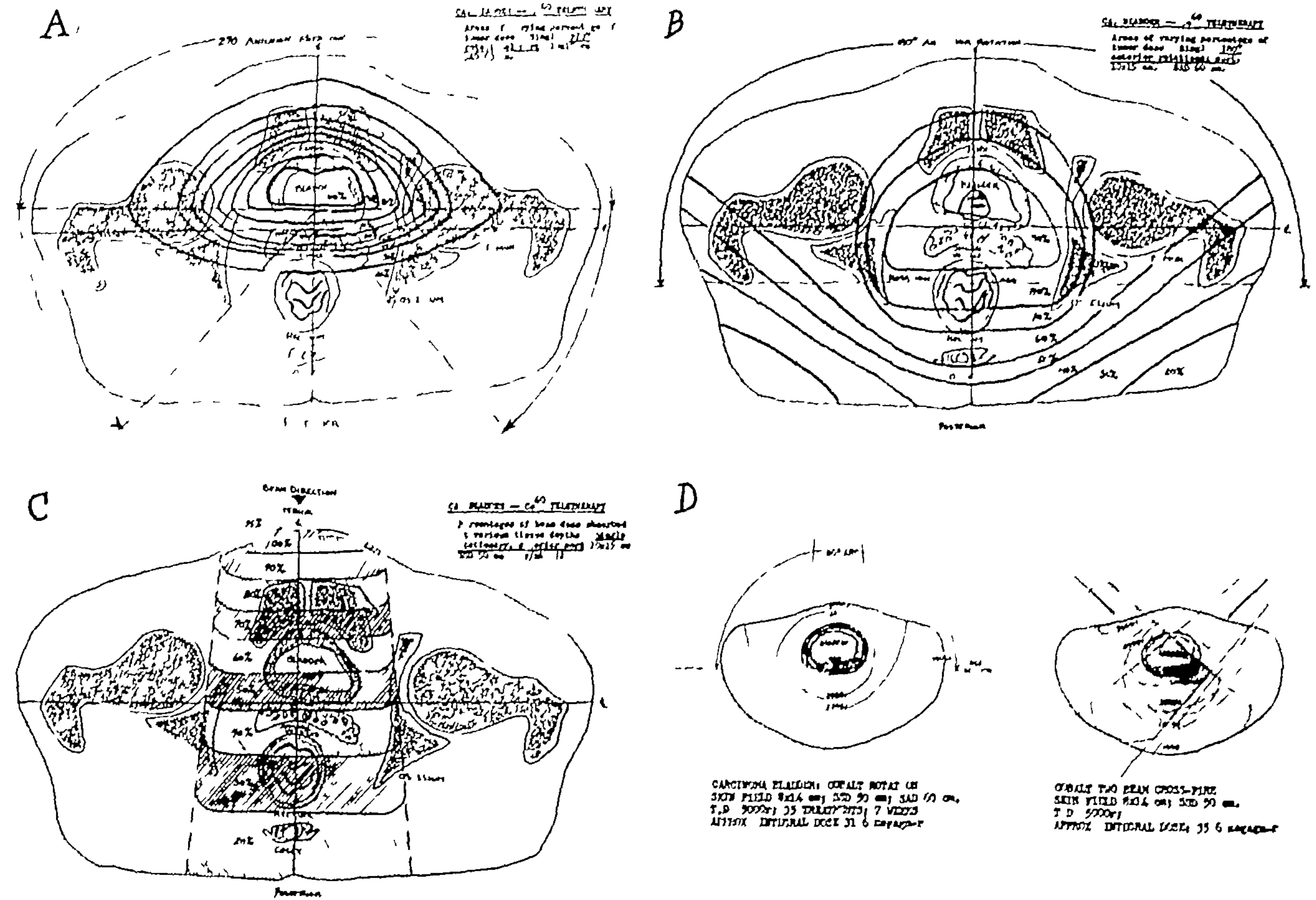


FIG 5 Lateral cystogram showing area covered by radiation beam Because beam does not include a sufficient area of tissue posterior to bladder, setup was corrected by moving beam posteriorly

structure such as air cavities The plastic phantom is made for each patient, and this is filled with a special bolus material which simulates body tissue specific density By placing a radiation recording instrument at the simulated tumor site in the phantom an actual treatment is given and the "tumor dose" is recorded By moving the radiation dosimeter to various areas about the tumor site an actual isodose pattern is determined When there is lymph node (fig 2) extension of the disease the volume of tissue to be irradiated is accordingly mapped out When no extension through the bladder or lymph node involvement is present, a much smaller tumor volume is irradiated

Our patients are usually treated in the vertical position on a specially constructed rotating chair (fig 3) The skin reaction which results after a tumor dose of 5,000 to 6,000r is given in six to eight weeks is only a faint erythema, as com-


A
B
C
D
Beam Direction
Bladder
Rectum
Posterior
100%
90%
80%
70%
60%
40%
30%
CARCINOMA BLADDER: COBALT ROTATION
SKIN FIELD 8x14 cm; SSD 50 cm; SAD 60 cm.
T.D 5000r; 35 TREATMENTS; 7 WEEKS
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COBALT TWO BEAM CROSS-FIRE
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T D 5000r;
APPROX INTEGRAL DOSE 35 6 megagm-r

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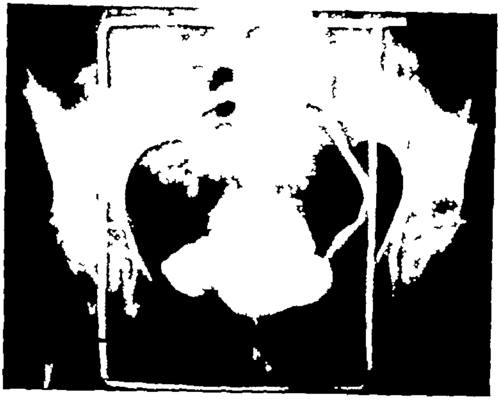

FIG 4 Anteroposterior cystogram with wire marker on patient's skin delineating area covered by the cobalt beam

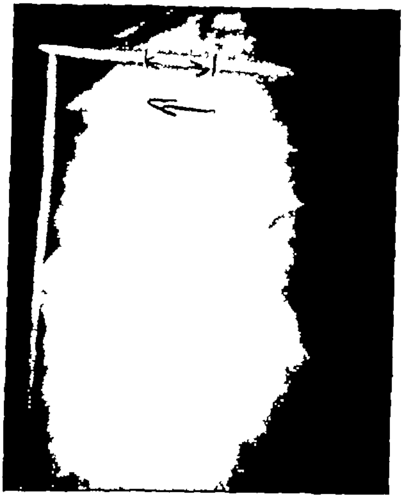

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TABLE 1 *Bladder-cobalt teletherapy Preliminary results, 36 cases*

	No	Trans	Adeno	Epid	Undif
Good	16	10	1	4	1
Fair	5	4	1	—	—
Poor	9	5	—	3	1
Incomplete treatment	3	3	—	—	—
Too early for eval	3	2	—	1	—
	36	24	2	8	2

TABLE 2 *Bladder-cobalt teletherapy Preliminary results, 36 cases*

	No	Stage				Living	Dead
		1	2	3	4		
Good	16	5	6	4	(1)*	15	1
Fair	5	—	—	3	(2)*	3	2
Poor	9	—	1	4	4	3	6
Incomplete treatment	3	—	—	3	—	—	3
Too early for eval	3	1	2	—	—	3	—
	36	6	9	14	7	24	12

* Deceased

bladder one of these had a good result, and one had only a fair result Eight patients had an epidermoid type of bladder tumor, four of these had a good result, three had a poor result, and one was treated of recent date Of the two patients with an undifferentiated type of tumor, one had a good result and one a poor result

Of the total 36 patients (table 2), six were in our clinical stage 1, five of these had a good result, while one has been treated of recent date This of course indicates that clinical stage 1 cases have an excellent prognosis because they do not have tumor involvement of the bladder wall Of the 9 patients in clinical stage 2 six had a good result one had a poor result and two patients were treated recently This also would indicate that the clinical stage 2 patients have a relatively good prognosis The 14 patients with more advanced disease in clinical stage 3 were the ones in whom we were particularly interested because these have usually had the worst prognosis in view of the fact that they have infiltrating tumors with penetration of the bladder wall and some with regional lymph node metastases Four of these showed a good result three had a fair result four had a poor result while three were too ill to complete their treatment Therefore it appears that about one-third of these patients might be salvaged with cobalt therapy Seven patients in clinical stage 4 were treated primarily at the beginning of our series in order to determine what effect cobalt radiation would have, since we knew that these patients would have postmortem examinations The autopsies pared to the very severe telangiectasia and skin atrophy which would result with half of this tumor dose if delivered by conventional x-ray therapy We check the location of the beam by making roentgenograms of the bladder after the instillation of radiopaque material (figs 4 and 5) A specially constructed diagnostic x-ray machine is attached to the cobalt machine so that these roentgenograms can be made to accurately check the size and direction of the beam

The following are various isodose patterns for cobalt-60 rotation therapy of the bladder

1) A 270° anterior rotation pattern (fig 6, *A*) shows that the 100 per cent zone is directly in the region of the bladder Only the anterior wall of the rectum is receiving about 20 per cent of the radiation dose This is of course a distinct advantage since the rectal reactions may become severe with other types of treatment and may therefore limit the total tumor dose

2) A 360° rotation pattern shows that the bladder and rectum are both in the 90 to 100 per cent zone, which is a distinct disadvantage The only possible advantage of this pattern is that a fairly large amount of radiation may be given to a larger volume of tissue When there is considerable disease extending outside of the bladder, a portion of the treatment may have to be given by this method and the remainder of the treatment by the 270° rotation

3) The 180° anterior rotation pattern (fig 6, *B*) again shows that the rectum received 70 to 80 per cent of the total dose However, a relatively large amount of perivesical tissue can be irradiated by this technique This technique may be combined with the 270° technique when there is extensive perivesical and lymph node involvement

4) When stationary techniques are employed either in single or multiple portal fashion, one must accept the fact that the radiation dose will be much higher to the subcutaneous tissues because the dose is 100 per cent immediately below the skin and gradually falls off toward the bladder region The skin dose is considerably less with rotation therapy than stationary cobalt therapy, but even with stationary cobalt treatment the skin dose is only one-third of what it would be with conventional x-ray treatment In the single port pattern when the beam is directed anteriorly (fig 6, *C*), the percentage of radiation as indicated shows that the bladder receives about 60 per cent of the dose, whereas the subcutaneous tissue receives 100 per cent of the dose It should also be noted that the rectum is receiving about 30 per cent of the dose and there is an exit dose of about 20 per cent through the posterior side of the body There is some danger of overlapping (fig 6, *D*) when multiple single ports are used

RESULTS

Thirty-six patients with bladder cancer have been treated and followed for almost three years (table 1) Twenty-four of these patients showed a transitional cell carcinoma, and of these, ten had a good result, four had a fair result, and five a poor result Three of these had incomplete treatment, and two have been treated of recent date Two patients had adenocarcinoma of the

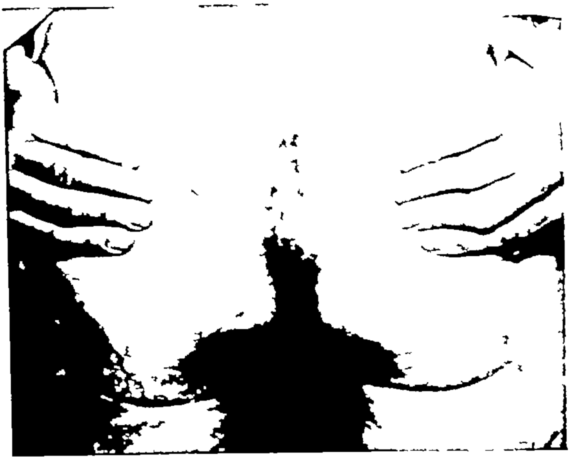


FIG 7 Carcinoma of prostate Intense skin reaction over sacrum because skin is at lower level than buttocks and therefore is in 100 per cent zone rather than 30 per cent zone of skin surface over buttocks

skin reaction (fig 7) developed over the sacrum because the folds of the buttocks caused the skin over the sacrum to be at a lower level than the skin of the buttocks Actually the skin over the sacrum was now in a "tumor position" rather than a skin position, since the intensity of the beam below the highest point was 100 per cent as compared with only 30 per cent on the skin surface

When the single beam was directed from the anterior (fig 8, *A*) part of the body the tumor dose in the prostate was about 50 per cent and the rectal dose only 40 per cent as compared to the rectal dose of 60 per cent and tumor dose in the prostate of 40 per cent when the beam was directed from the posterior aspect (fig 8 *B*) It is therefore apparent that the anterior beam of the single portal is more efficient than the posteriorly directed single beam Because of the large dose to the rectum we therefore had to give up the single portal technique and rely on rotation therapy

With 180° anterior rotation (fig 8 *C*) technique the prostate received 100 per cent of the dose while the rectum received 80 to 90 per cent of the dose With the 360° rotation both the prostate and rectum again were in the 90 to 100 per cent dose range With the 270° anterior rotation (fig 8, *D*), the prostate received 100 per cent of the dose while the rectum received from 40 to 60 per cent of the dose It is apparent that there is no way to spare the rectum completely because of the close proximity of the prostate to the rectum anatomically We now combine the anterior single port technique for about half the total dose and then give the remainder of the treatment between 270° anterior rotation or the 360° anterior rotation (fig 9), depending on the lateral extent of the disease At the time of the original surgical exploration and isotope injection the presence of metastatic lymph nodes is determined (fig 10) and if present they must be included in the field of radiation of the cobalt team of these patients revealed that one had a good result as far as the local disease was concerned Our pathologist could not find any residual evidence of cancer in the area covered by the cobalt beam Of course, this patient had extensive liver and bone metastases, and these areas were not treated Two of the patients examined post mortem showed a fair response, while four showed a very poor response This further emphasizes that the cobalt beam is capable of causing destruction of the tumor tissue at the bladder site and also in the perivesical and lymph node tissue in a small percentage of patients Altogether, 24 of the 36 patients in this series are alive, while 12 are dead Of the living patients, 15 had a good result, three had a fair result, three had a poor result, while three have been treated recently Of the 12 deceased patients, one had a good result, two had a fair result, six had a poor result, and three did not complete their treatment

COMPLICATIONS

There were no serious complications noted during treatment or after treatment The patients who do not have extensive bladder wall infiltration and penetration show relatively little bladder contraction following treatment as compared to the bladder contraction which we often observed after conventional x-ray therapy The rectal complaints which are at their peak at the conclusion of the treatment series usually last for about two to three weeks The skin reactions at their peak are only a mild erythema, and later mild tanning The skin remains soft and pliable, and in only one case did we observe a postradiation fat necrosis In this patient all the treatment was delivered through a single anterior portal so that the subcutaneous fat received the largest part of the dose When patients had previously been treated with radon seeds or radium needles and then referred to us several years later for recurrent disease we found that a radiation necrosis would often develop at the site of the previous interstitial radiation When years elapse between radiation treatments the blood supply of the local area is impaired and these local areas may not stand up too well under further heavy irradiation When local radiation necrosis develops in such cases it usually responds to local therapy and sometimes the use of meticorten is helpful

PROSTATIC CARCINOMA

Our previous communications reported our technique and results for the colloidal chromic phosphate palliative treatment of advanced prostatic cancer Although we have been impressed with the results from a palliative standpoint, it became obvious that some patients required more than local injection treatment, since post-treatment biopsies and clinical examination of some of these patients confirmed the presence of further growth of tumor Instead of re-injecting these patients with more chromic phosphate at three to four month intervals, when disease was found on post-treatment biopsy we have elected to treat a group of these patients secondarily with cobalt bomb rotation therapy When single port posterior techniques were first used we noted that a serious and severe

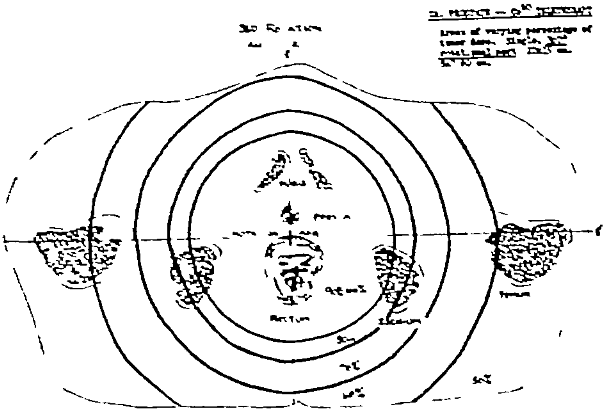


FIG 9 Carcinoma of prostate treated by cobalt bomb showing dosage pattern with 360° rotation

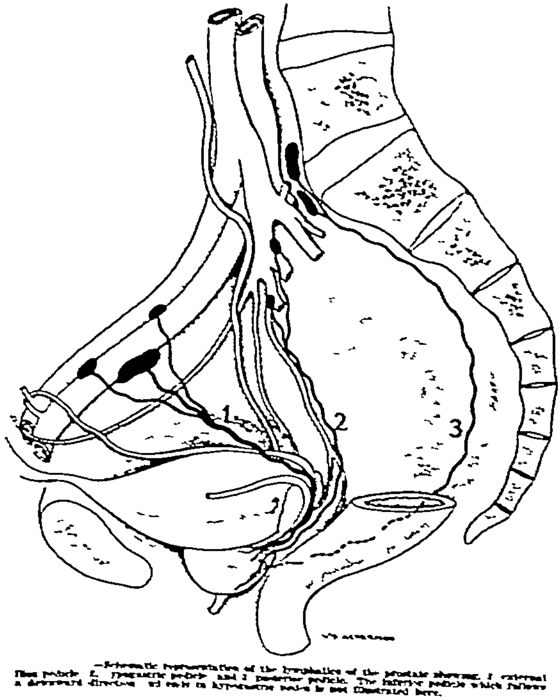


FIG 10 Sketch showing lymphatic drainage from prostate

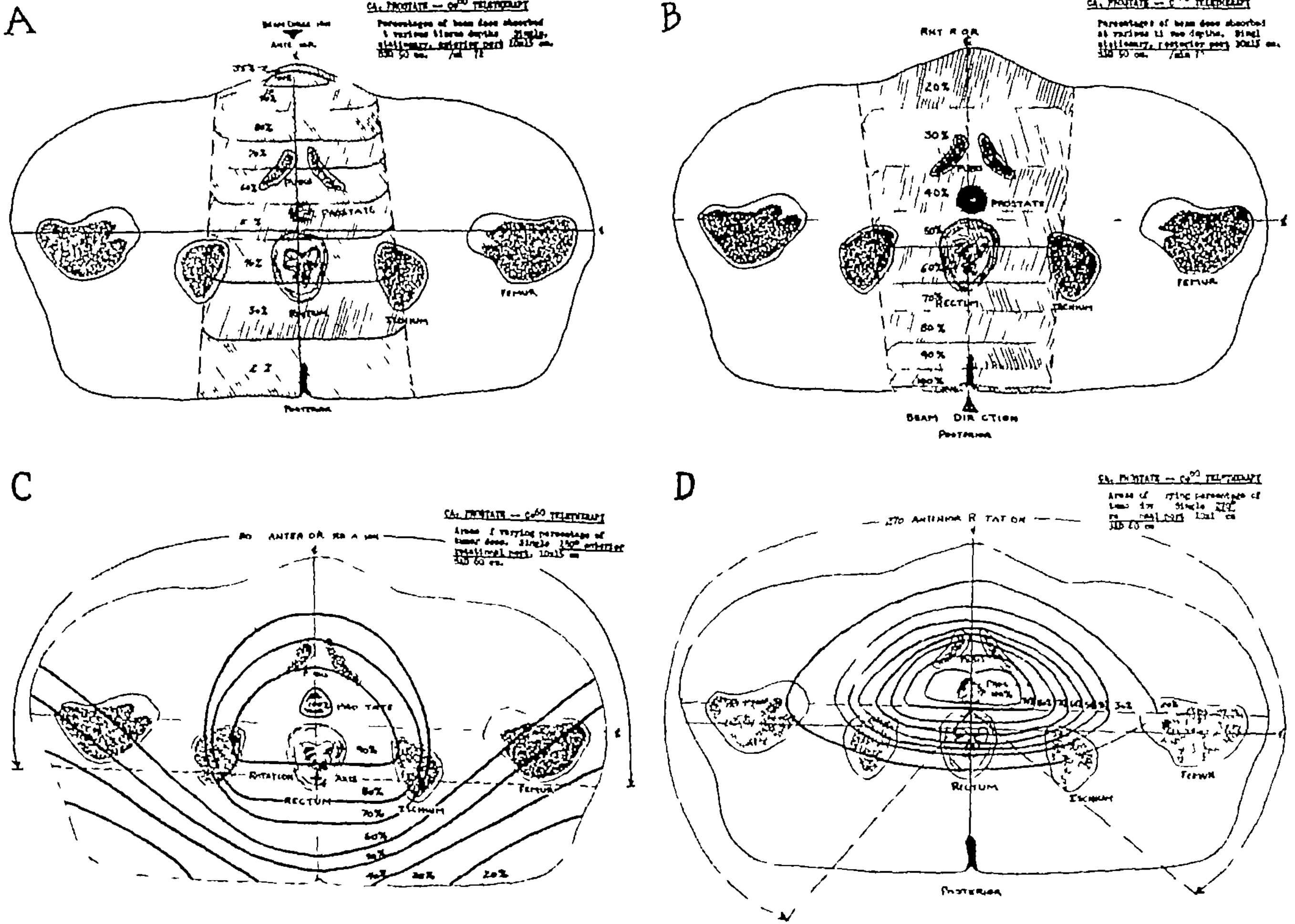


FIG. 8. Carcinoma of prostate. A, single anterior beam shows 50 per cent tumor dose in prostate area and 10 per cent in rectum. B, single posterior beam shows 10 per cent of radiation dose in prostate and 60 per cent in rectum. C, treated by cobalt bomb, showing dosage pattern with 180° anterior rotation. D, treated by cobalt bomb showing dosage pattern with 270° anterior rotation.

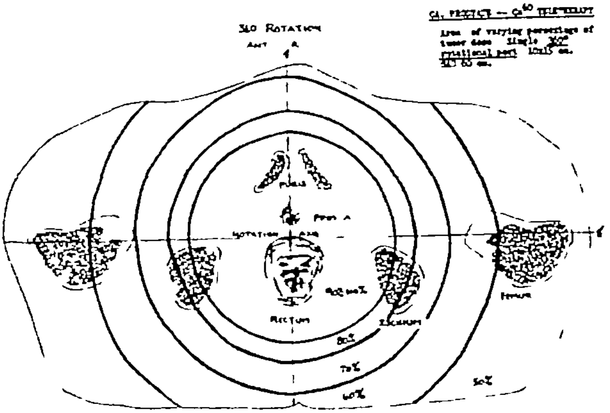
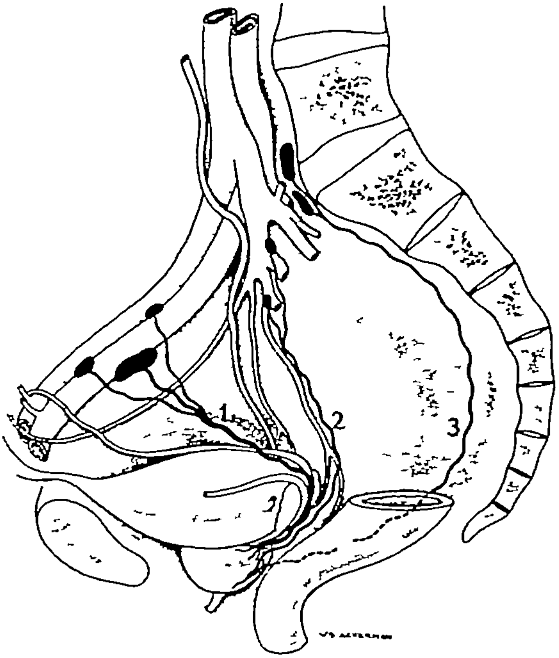


FIG 9 Carcinoma of prostate treated by cobalt bomb, showing dosage pattern with 360° rotation



—Schematic representation of the lymphatics of the prostate showing, 1 external iliac pedicle, 2, hypogastric pedicle and 3 posterior pedicle. The inferior pedicle which follows a downward direction and ends in hypogastric nodes is not illustrated here.

FIG 10 Sketch showing lymphatic drainage from prostate

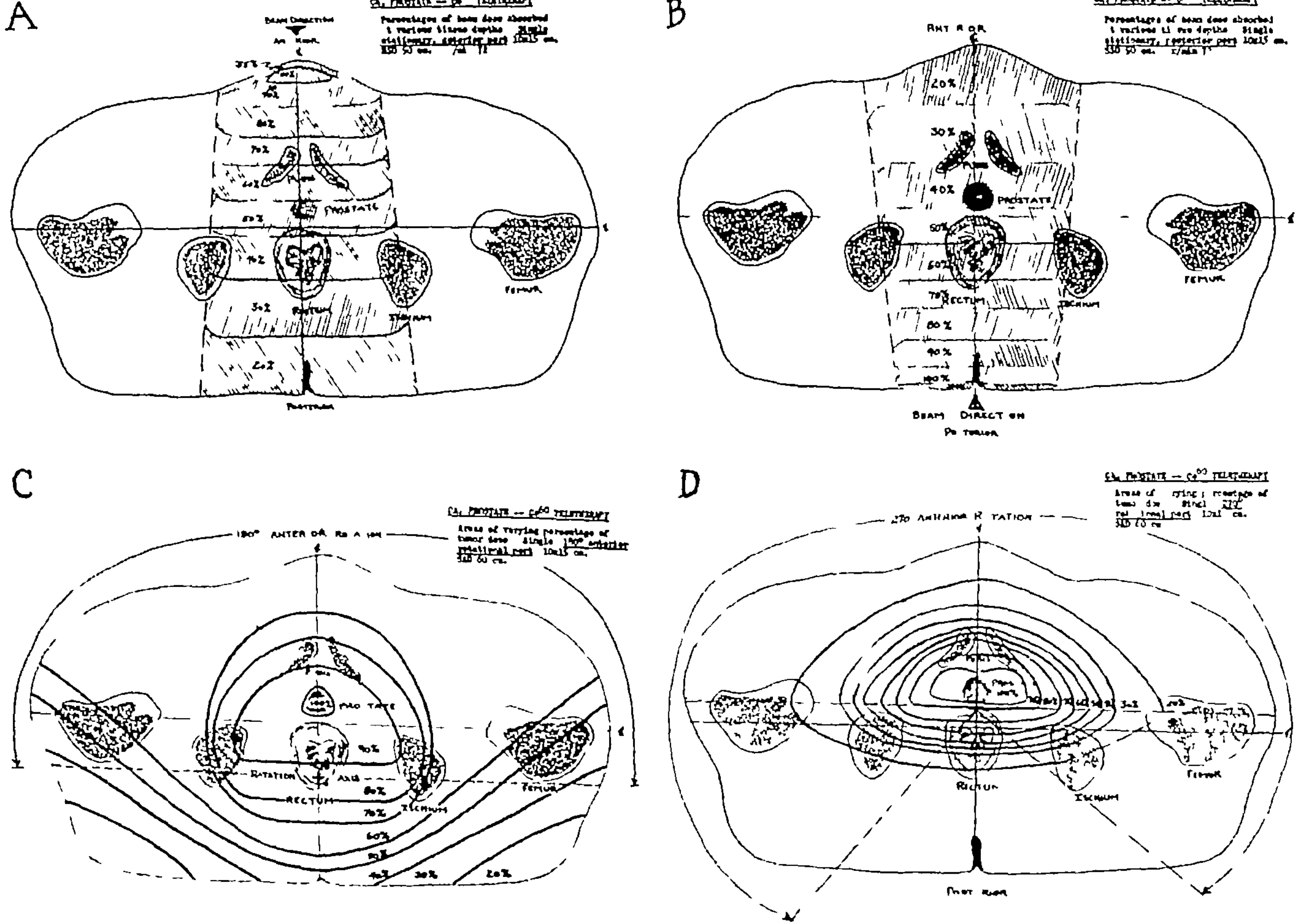

A
B
C
D
Ca. PROSTATE
Percentages of beam dose absorbed at various tissue depths. Single stationary, anterior port 10x15 cm.
Percentages of beam dose absorbed at various tissue depths. Single stationary, posterior port 10x15 cm.
Ca. PROSTATE — Co60 TELETHERAPY
Areas of varying percentage of tumor dose. Single 180° anterior rotational port 10x15 cm. SSD 60 cm.
Areas of varying percentage of tumor dose. Single 270° rotational port 10x15 cm. SSD 60 cm.
BEAM DIRECTION
BEAM DIRECT ON PO TUMOR
180° ANTERIOR ROTATION
270 ANTERIOR ROTATION
PROSTATE
RECTUM
FEMUR
ISCHIUM
ROTATION AXIS
20%
30%
40%
50%
60%
70%
80%
90%
100%

FIG. 8. Carcinoma of prostate. A, single anterior beam shows 50 per cent tumor dose in prostate area and 40 per cent in rectum. B, single posterior beam shows 40 per cent of radiation dose in prostate and 60 per cent in rectum. C, treated by cobalt bomb, showing dosage pattern with 180° anterior rotation. D, treated by cobalt bomb, showing dosage pattern with 270° anterior rotation.

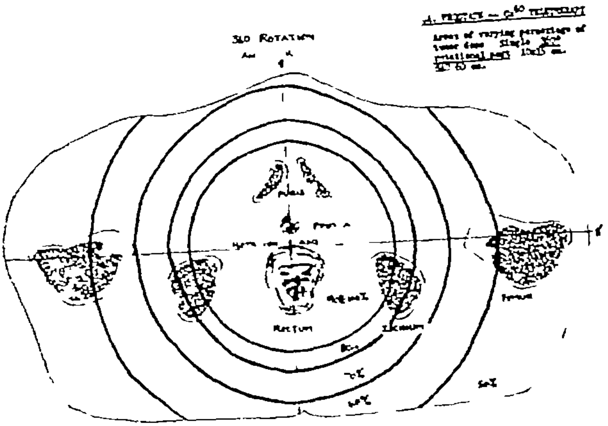


FIG 9 Carcinoma of prostate treated by cobalt bomb, showing dosage pattern with 360° rotation

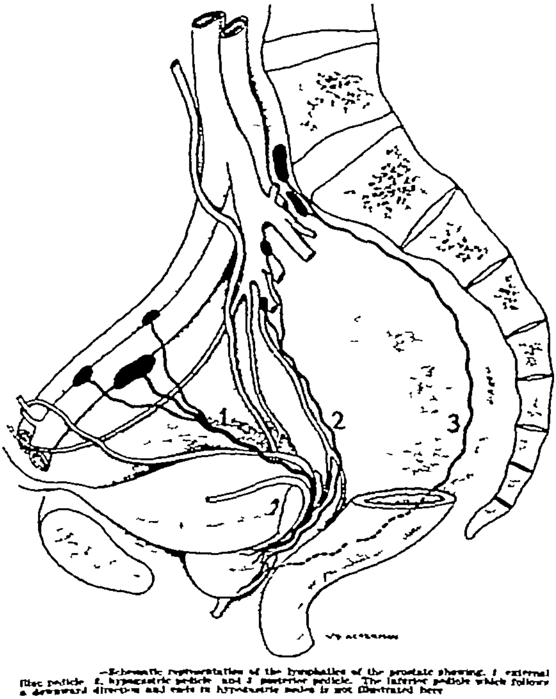

1
2
3
—Schematic representation of the lymphatics of the prostate showing, 1 external iliac pedicle, 2, hypogastric pedicle and 3 posterior pedicle. The inferior pedicle which follows a downward direction and ends in hypogastric nodes is not illustrated here

FIG 10 Sketch showing lymphatic drainage from prostate

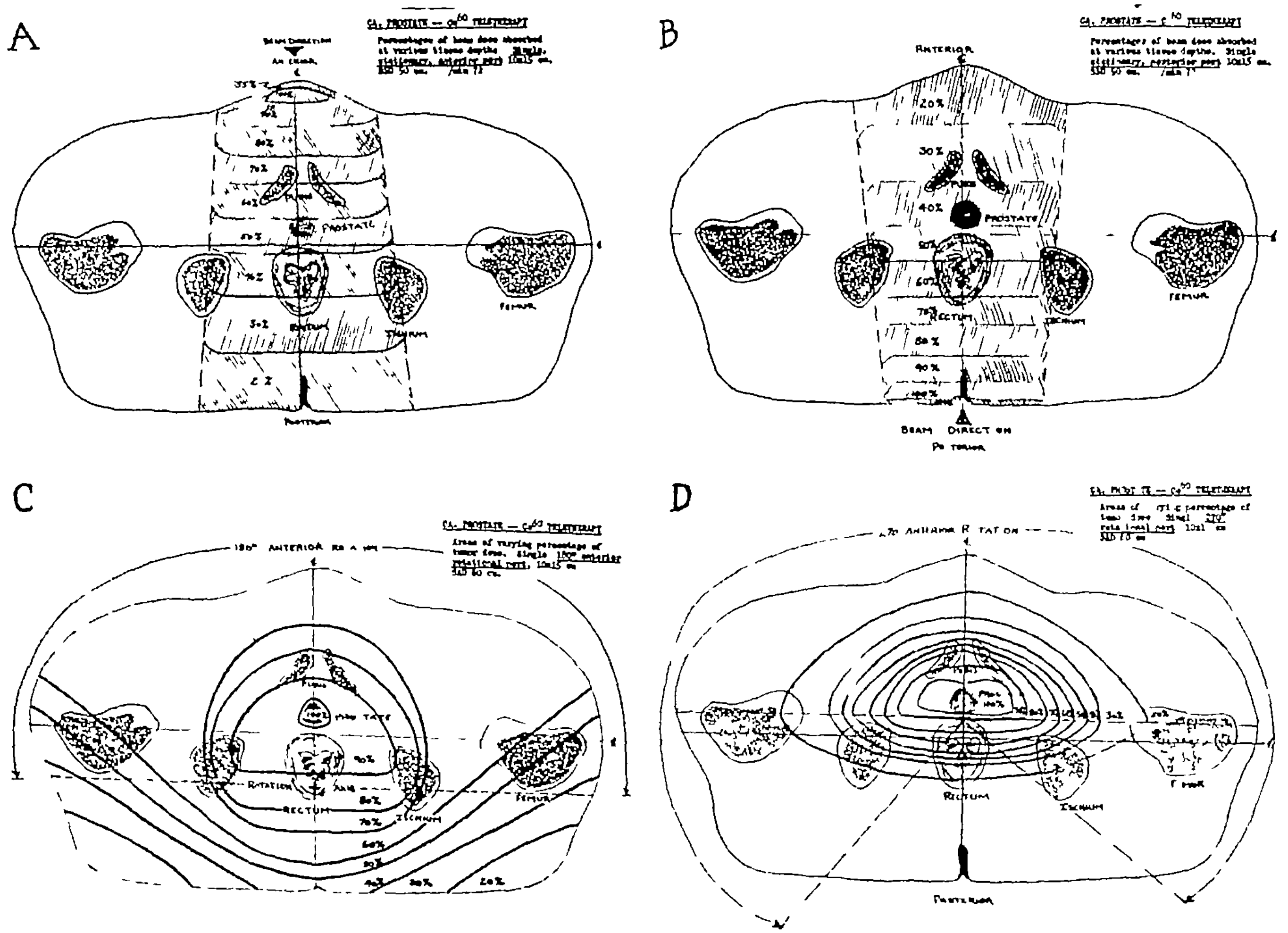

A
B
C
D
CA. PROSTATE — Co60 TELETHERAPY
Percentages of beam dose absorbed at various tissue depths. Single stationary, anterior port 10x15 cm. SSD 50 cm.
Percentages of beam dose absorbed at various tissue depths. Single stationary, posterior port 10x15 cm. SSD 50 cm.
Areas of varying percentage of tumor dose. Single 180° anterior rotational port, 10x15 cm. SSD 60 cm.
Areas of varying percentage of tumor dose. Single 270° rotational port. 10x15 cm. SSD 60 cm.
BEAM DIRECTION
ANTERIOR
PUBIS
PROSTATE
RECTUM
ISCHIUM
FEMUR
POSTERIOR
BEAM DIRECT ON PO TUMOR
180° ANTERIOR ROTATION
270 ANTERIOR ROTATION
ROTATION AXIS
20%
30%
40%
50%
60%
70%
80%
90%
100%

Fig. 8. Carcinoma of prostate. A, single anterior beam shows 50 per cent tumor dose in prostate area and 10 per cent in rectum. B, single posterior beam shows 40 per cent of radiation dose in prostate and 60 per cent in rectum. C, treated by cobalt bomb showing dosage pattern with 180° anterior rotation. D, treated by cobalt bomb, showing dosage pattern with 270° anterior rotation.

normal tissues This was impossible when we used conventional 200 to 250 KV therapy machines

The immediate results are sufficiently encouraging so that we feel that we should continue this procedure

There is a striking absence of secondary contracture of the bladder following cobalt bomb therapy as compared to the bladder contracture which usually follows intensive conventional x-ray therapy

1400 N Vermont Ave , Los Angeles 27, Calif (C F R)

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* Arranged chronologically

TABLE 3 *Prostate cobalt teletherapy Results, 15 cases*

	No	Living	Dead
Good	8	7	1
Fair	3	2	1
Poor	4	1	3
	15	10	5

RESULTS

Of the 15 patients who received cobalt bomb therapy for advanced prostatic cancer (table 3), 13 had a combination of the isotope injection followed by cobalt bomb therapy, while two patients received only cobalt bomb therapy Of the 15 patients treated, eight showed a good result, seven of these are living and one is dead Three patients showed a fair result, two of these are living and one is dead Four patients had a poor result following this treatment, and of these one is living and three are dead It therefore appears that at least two-thirds of the patients have had a worthwhile result to date

COMPLICATIONS

No serious complications have occurred since we have adjusted the technique to avoid the severe skin reactions which we noted when the patients received all of the treatment through a single posterior port technique Rectal edema and radiation reaction are apparent toward the completion of the total course of treatment when the patient has received about 5,000 to 6,000r tumor dose in six to eight weeks This lasts for about two to three weeks and then subsides During the height of the reaction the patient complains of diarrhea, but this is controlled by suitable medication and is only of short duration We have not observed any serious depression of the bone marrow with this type of irradiation When there is evidence of bone marrow depression it usually indicates that the patient has metastases to the bones, even though the x-ray examination of the bones may be negative A sternal puncture or bone marrow study of the iliac crest may reveal the presence of bone metastases before there is roentgen evidence of bone involvement by the disease

SUMMARY

A method of isotope treatment employing both the injection of radioactive colloidal chromic phosphate and the use of external cobalt bomb therapy is presented for the treatment of advanced bladder and prostatic cancer

If properly applied, this combined method of isotope treatment is well tolerated by the patient and does not appear to produce any serious complications

The radiation reaction in the skin is minimal and there is relative absence of radiation sickness, in spite of the fact that a very large tumor dose is delivered

It is now possible to deliver high tumor doses by the combined isotope treatment and the cobalt bomb therapy, and it is also possible to accurately direct this treatment to the involved tissues with minimal damage to the surrounding

Their radioisotopic method was cumbersome and complicated However, the findings reported stimulated this investigation

SUBJECTS AND PLAN OF INVESTIGATION

The subjects studied were consecutive individuals needing prostatectomy while patients in the San Diego County General Hospital Volumetric, gravimetric, and radioisotopic methods were adopted to determine gain or loss of weight and fluid during the operation Thus the accuracy of each method could be compared with the others Absorption of the radioisotope was obtained by direct detection with a scintillator head placed over the heart of the patient It was hoped that the study would result in clinically useful findings

MATERIALS AND EQUIPMENT

For the gravimetric portion of the study, a beam scale accurate to ¼ oz was obtained from the Howe Scale Company This was adapted to our use by placing it upon a special table that could support a litter top and patient (fig 1) The same scale was used to determine the weight of the drapes both preoperatively and postoperatively Three 19 liter carboys were calibrated with volumetric flasks and retained as measures for the entire series These were attached by a closed system to the percolators, which were maintained at a constant height of

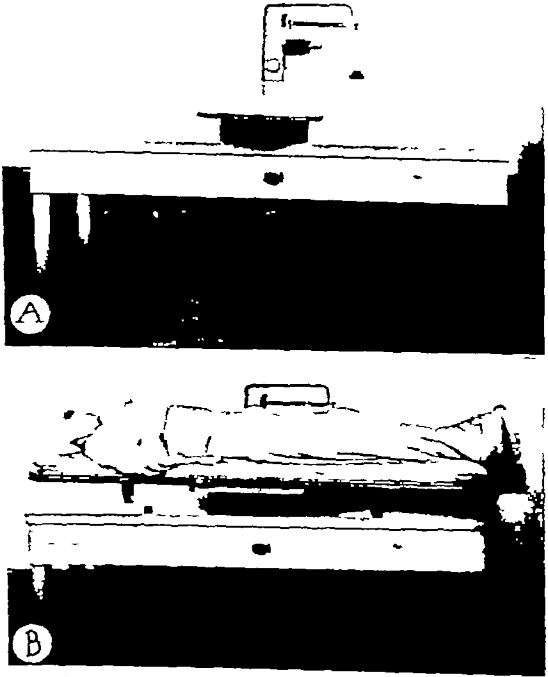

Fig 1 A beam scale accurate to ¼ oz B method of weighing patient with litter top

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VOLUMETRIC, GRAVIMETRIC AND RADIOISOTOPIC DETERMINATION OF FLUID TRANSFER IN TRANSURETHRAL PROSTATECTOMY

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It is generally accepted that intravascular infusion and hemolysis is a distinct possibility during transurethral surgery Creevy[1] has shown that isotonic irrigating solutions have reduced the mortality rate from 3–4 per cent to 0 96 per cent Creevy and others,[2, 3] using isotonic glucose irrigating solution, proved that infusion occurs by finding elevated blood sugar levels and positive blood cultures These facts alone have caused the acceptance, by most urologists, of nonhemolytic isotonic irrigating media

The authors sought to determine accurately the volume of fluid absorption during transurethral prostatectomy Previous methods were reviewed Landsteiner and Finch,[4] using clinical observation and gross laboratory tests, estimated that one of their patients received at least 1,000 cc by this route Murphy, Iob and Lapides[5] studied fluid and electrolyte balance before and after operation of 11 patients, and found no alteration Bulkley and associates,[6] and Hagstrom[7] have reported sudden heart failure in patients with pre-existing cardiac lesions, and in others, unexpectedly high urine output, following transurethral resection They attributed this to the absorption of large volumes of fluid through the prostatic veins Harrison[8] and associates estimated that patients undergoing transurethral prostatectomy would become agitated when about 3,000 cc fluid were infused, and also noted a change in the postoperative electrolytes in such a patient

The first adequate attempt to measure intravascular irrigating fluid transfer was undertaken by Griffin and associates [9] They found that as much as 3,950 cc fluid could be so absorbed They measured fluid absorption volumetrically and by radioisotope tagging The patients selected were in good physical condition

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Read at annual meeting of Western Section of American Urological Association, Seattle, Wash , May 27–30, 1957

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was carefully noted The returning irrigating fluid was meticulously retrieved by an assistant Accidental spillage of irrigant was absorbed by floor coverings weighed previously The operations were done by the resident staff of the San Diego County General Hospital and extensive resections were done intentionally

The operator would note the area of resection and report to the technician

TABLE 1 *Tabulation of results obtained by volumetric radioisotopic and gravimetric portions of study*

	Age	Volume Absorbed cc	Weight Increase Gms	Radioactivity Increase Cpm	Increase B P	Mental Agitation	Length Resection Minutes	Tissue Removed Gms
				Sinus(es) open				
G K	67	745	361	400	yes	no	118	20 1 F
*P C	85	3430	2892	—	yes	yes	40	33 B
Z H	88	3499	3365	2535	yes	yes	40	8 C
C B	78	864	414	—	no	yes	75	33 C
J H	75	2551	2710	—	yes	no	120	29 5 B
F S	74	943	597	—	no	no	64	23 B
H M	52	1610	1099	—	no	no	47	12 F
W S	68	2258	2058	1820	no	yes	73	68 C
J V	69	1249	866	1450	no	no	54	2 4 BN
J S	71	505	542	550	no	no	74	39 7 B
				No open sinus				
J C	88	158	−130	30	no	no	80	64 3 B
J R	78	121	39	180	no	no	18	2 5 BN
G K	67	192	−151	55	no	no	85	54 1 B
E I	72	20	−72	65	no	no	68	14 6 B
A O	79	2499	2428	—	yes	no	50	5 F
A H	77	774	−117	180	yes	yes	44	17 B
T B	79	211	−112	30	no	no	54	12 B
R B	65	472	455	—	no	no	53	14 B
W H	75	45	−24	0	no	no	68	12 F
R S	54	1440	1626	—	no	no	53	16 B
J V	69	163	16	0	no	no	43	7 F
E W	98	657	−88	—	no	no	50	18 5 B
R G	73	731	−196	0	no	no	45	22 B
A E	74	359	86	—	no	no	72	32 B
J M	78	1257	1400	—	no	no	76	44 B

*—Expired 2nd P O day B—Benign F—Fibrotic C—Carcinoma BN—Bladder Neck Contracture Cpm—Count per minute

TABLE 2 *Incidence of appearance of signs of fluid absorption as related to presence of open sinuses*

Patients known to have open sinuses	10
Patients with no open sinuses but periprostatic fat showing	1
Sinus open no blood pressure rise	4
Sinus open rise in blood pressure	4
Sinus open no blood pressure rise but pulse slowed	2
No sinus open but blood pressure rise	1

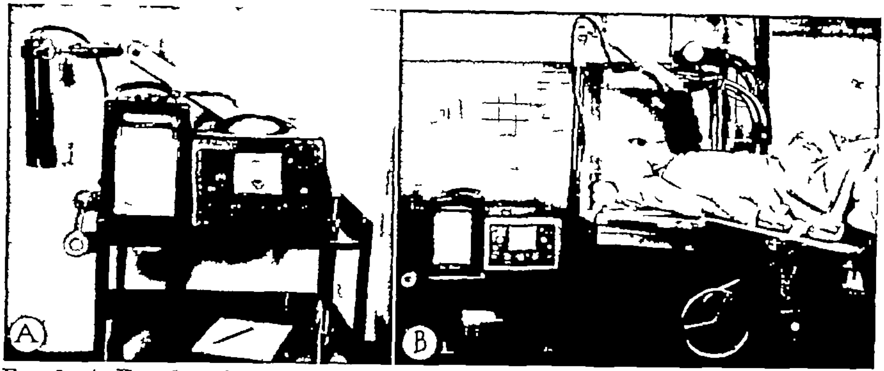

FIG 2 *A*, Esterline Angus recorder, count rate meter and scintillator head *B*, system for detecting radioactivity in position over patient

28 inches above the operating table level To detect the activity of the tracer-labelled irrigating fluid as it entered the circulation of the patient, a scintillator head (Nuclear Chicago), a count rate meter (Nuclear Chicago), and a direct writing recorder (Esterline-Angus) were used (fig 2) The scintillator head was placed at the skin level of the patient at the fifth interspace just to the left of the sternal border The radioisotope used was sodium iodide^{131} (Oriodide, sterile, Abbott)

METHOD

All candidates received careful preoperative evaluation which includes medical consultation whenever indicated Two days prior to surgery, patients were given potassium iodide as a blocking agent to the thyroid gland Preoperative preparation included 500 mg of terramycin the night before and the morning of surgery The irrigation solution was prepared by adding the NaI^{131} to the previously measured 1 1% glycine solution

The radioactive isotope, in a concentration of 26 microcuries per liter, was used as the isotope tag This concentration was selected empirically after it was found that it would give, roughly, one count per minute per cc of absorbed fluid One thousand cc of 5% dextrose in water containing 26 microcuries of I^{131}, when given intravenously, would cause an increase in activity over the heart of about 1,000 counts per minute To rule out the possibility of absorption of the I^{131} from the bladder and intact prostate, a control study was made with the bladder filled with the tagged irrigating solution No absorption was detected, this bears out the findings of others[10]

En route to the operating room, the patient was weighed with the catheter he would have postoperatively The actual measurement was done by weighing the litter top and patient on the special scale The patient was given a low spinal or saddle anesthesia, 5% dextrose in distilled water was started by slow intravenous drip The scintillator head was then positioned over the patient's heart and the background count determined Cystoscopy was started using the Iglesias-Torre modification of the Nesbit resectoscope The time of the first incision

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DATA

The twenty-five patients studied presented an average age of 74.2 years. One death occurred. The average weight of tissue resected was 25.2 gm., with a range of 2.4 to 68 gm. The average blood loss was 282 cc. of whole blood with a range of 21 to 790 cc. Seventeen patients (68%) showed definite evidence of fluid absorption, while the remaining eight (32%) exhibited loss of body weight during the procedure. Of those showing absorption, the average weight gain was 1,225 gm. and an average loss of irrigating fluid of 1,335 cc. See table 1 for

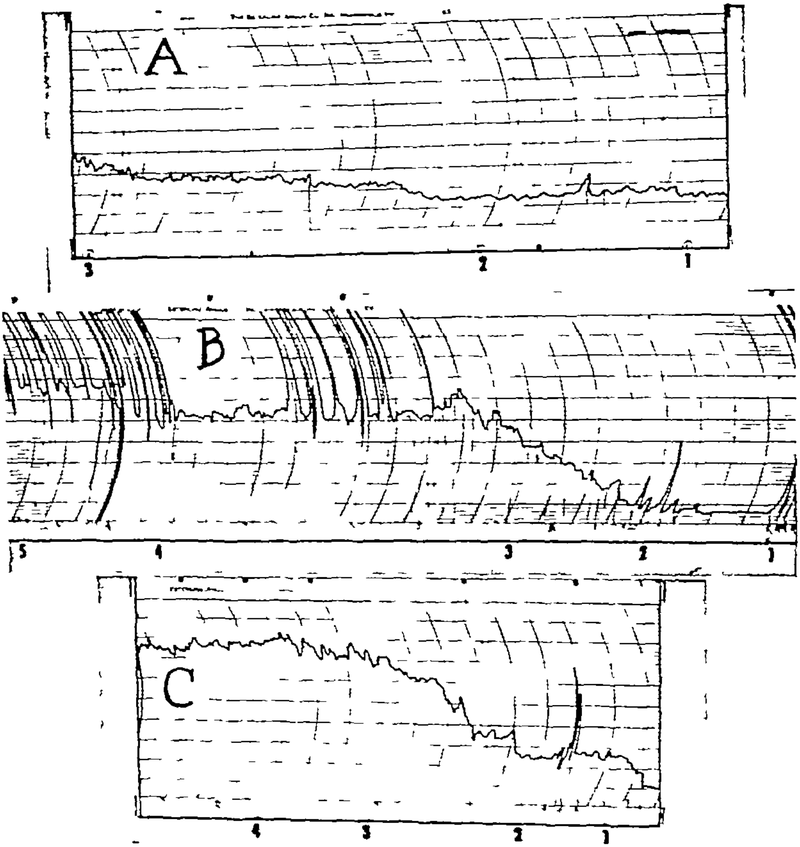

FIG. 5. A, correlation of radioisotopic detection of irrigating fluid absorption, gain in body weight and loss of irrigating fluid as measured volumetrically. 1, Start of operation. 2, Sinus open. 3, End of operation. Weight of tissue 39 gm. Weight gain, 542 gm. Fluid absorbed 505 cc. Increase in radioactivity 550 cpm.

B, actual tracing obtained during prostatectomy. Spikes indicate interference. 1, Start of operation. 2, Venous sinus open. 3, Second sinus open. 4, Interference. 5, End of operation. Weight of tissue 68 gm. Weight gain 2258 gm. Fluid absorbed 2058 cc. Increase in radioactivity 1820 cpm.

C, Note relationship of open sinuses and increase in rate of fluid absorption. Extensive resections done in all cases. 1, Start of operation. 2, Large sinus open. 3, Three sinuses open. 4, End of operation. Weight of tissue 2.4 gm. Weight gain 1201 gm. Fluid absorbed 1249 gm. Increase in radioactivity 1450 cpm.

any unusual bleeding or the presence of sinuses These were then noted on the continuous tracing of the radioactivity passing through the heart The anesthetist would report any change in the patient's condition and this too was recorded

At the termination of the procedure, all values such as intravenous fluids, pontocaine, diluent, tissue weight, water in the Foley catheter bag, and KY jelly were carefully recorded The patient was then returned to the scale and again carefully weighed, as were the drapes Any change in the irrigating fluid volume and the loss of blood was carefully determined Blood loss was determined by a Fischer hemometer which had been calibrated for use with the glycine solution and blood mixture The whole blood was converted to acid-hematin and the percentage of hemoglobin present determined directly, and the volume of blood loss calculated Corrections for urine and insensible fluid loss were determined by assuming 1 cc urine excretion per minute, and 0 5 cc insensible loss per minute as an average output

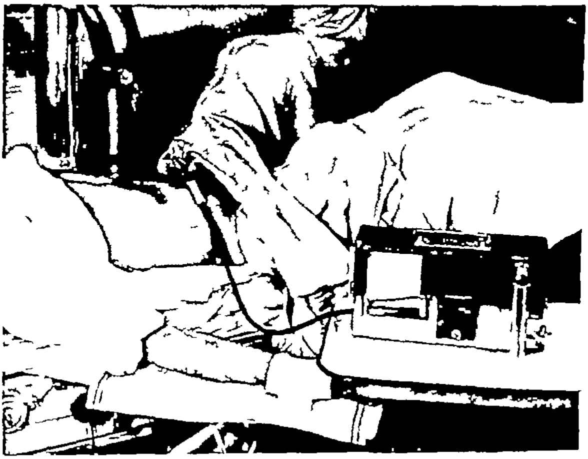

FIG 3 Lewis recording cystometer connected to suprapubic catheter Continuous tracing was made of intravesical pressure during transurethral prostatectomy

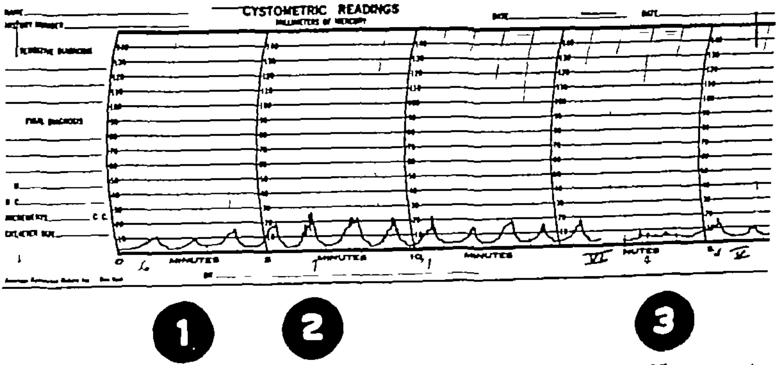

FIG 4 Actual example of tracing obtained with Lewis cystometer Note greatest pressure occurs with normal filling of bladder as occurs during transurethral prostatectomy *1*, Emptying and filling bladder *2* 23 mm Hg pressure, bladder full *3* 4 to 8 mm Hg pressure, Toomey syringe

fluid and the body weight change can only be explained by the evaporation of fluid inadvertently spilled during the resection The output of urine and the insensible loss were determined by the length of the operation By keeping as many of the variables as constant as possible it is felt that a reasonably accurate study has been made

After exposure to the radioisotope, the patients would maintain high levels of activity in the circulating bloodstream for as long as 12 hours Activity in the thyroid was sufficiently great with the early patients that later ones received adequate doses of iodine to block radioactive iodine uptake

The results of the study show that the patient may receive as much as 3 400 cc of irrigating fluid intravascularly during the course of transurethral prostatectomy Using three methods of evaluation simultaneously we have found a definite correlation of absorption of the irrigating fluid and the presence of open venous sinuses Rapid rise of the radioactivity in the circulating blood stream and the noting of the open sinuses by the operator were concomitant However, three patients (A O , R S , J M) received large amounts of fluid although no venous sinuses were observed This indicated that the surgeon was not always a good judge of fluid accumulation It follows that it is dangerous to use distilled water irrigation until obvious sinuses are opened

It is possible that electronics engineers could develop a small and compact scintillator head and count rate meter that could be attached to the patient s chest This would function like the cardioscope and would give the anesthetist and surgeon warning of excess absorption

The data indicate no true correlation between the type of gland resected and the amount of intravascular infusion Our observations suggest that patients with carcinoma of the prostate are prone to suffer greater infusion A larger series is necessary for confirmation Neither gland size histopathology nor type of enlargement gave forewarning as to which patients would absorb fluid Our findings substantiate those of others that most of the infusion occurs when the capsule is approached and venous sinuses are opened We found no evidence that any appreciable absorption takes place early in the removal of a benign adenoma

The removal of any form of prostatic obstruction may result in intravascular infusion of irrigants The experienced surgeon when close to the capsule, is less likely to have absorption occur Medium to large glands (40 gm or more) may develop thin capsules from the nature of the hypertrophy Theoretically this would increase the likelihood of entering the venous sinuses, especially if the bite of the loop is too generous Small fibrous glands may have stones in the capsule in attempting to unroof these, venous sinuses may be entered The anatomy of the neoplastic prostate is distorted, causing difficulty in identifying the capsule and increasing the chance of sinus incision

Until an electronic substitute is developed, three clinical signs can be used to observe significant absorption 1) slowing of the pulse 2) rise in both the systolic and diastolic pressure and, finally, 3) mental agitation of the patient If the anesthetist is aware of this chain of events he can warn the surgeon that dangerous overloading of the circulation is taking place

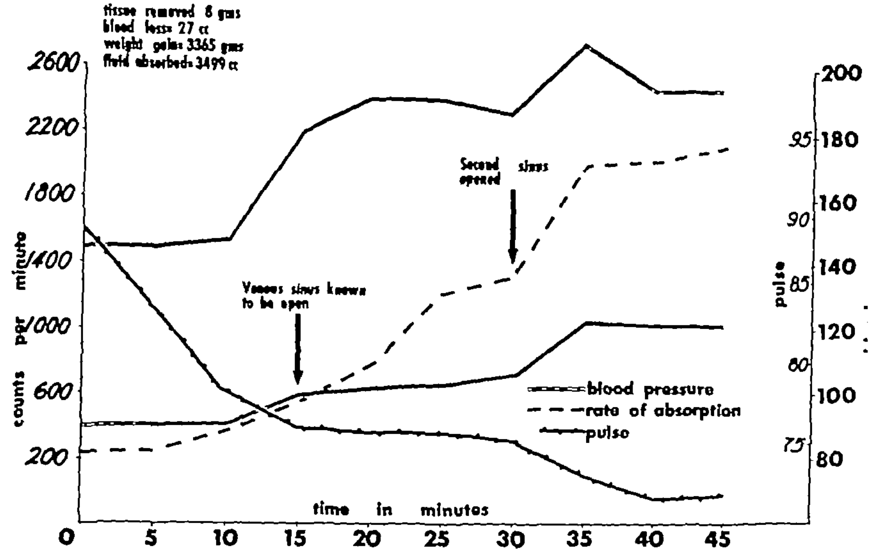

FIG 6 Graph shows actual detection of radioactive irrigating fluid and its effect pulse and blood pressure Note slowing of pulse followed by rise in blood pressure Pat became extremely restless at termination of procedure

tabulated results of the gravimetric, radioisotopic, and volumetric determ tions

Ten patients were known to have one or more open venous sinuses and had periprostatic fat showing, but no sinuses could be identified (table 2) patient (J V) with primary contracture of the bladder neck, absorbed no fl during his initial operation During a second operation for recurrent blad neck contracture, multiple sinuses were opened causing marked infusion second patient (G K), with an indwelling suprapubic tube, had an incompl operation On completion of his prostatectomy, sinuses were opened and body weight increased 360 gm During each of his two operations, a Le recording cystometer was connected to his suprapubic catheter allowing c tinuous intravesical pressure recordings (fig 3) Filling the bladder produ pressures as high as 23 mm of Hg while vigorous irrigation of the bladder w either the Toomey syringe or the Ellik evacuator produced intravesical pr sures of only 8 mm of Hg (fig 4)

Figure 5 shows the amount of radioisotope accumulated in the vascular syst as recorded directly during the various stages of the prostatectomy Figur illustrates the effect of fluid absorption on the blood pressure and pulse

The one patient who died developed acute pulmonary edema while on t operating table after absorbing almost 2,900 cc of irrigating fluid The p monary edema was corrected, but the patient developed irreversible circulato collapse, expiring on the second postoperative day

DISCUSSION

(4) High intravesical pressures appeared to increase intravascular infusion if sinuses were open

(5) Pressure evacuators do not increase absorption

(6) Open sinuses near capsule increase infusion rate

(7) So-called poor cardiac risk patients can withstand surprising amounts of infusion

(8) Appreciable amounts of irrigation fluid entered the vascular systems in 68% of the patients

(9) Three simple clinical signs of intravascular infusion are a) bradycardia b) rise in blood pressure c) agitation

(10) Appreciable absorption may occur though the operator is unaware that venous sinuses are open therefore isotonic irrigants should be employed from the beginning of the resection

(11) There is no absorption from the intact bladder and prostate Careful attention to the details demonstrated in this study should make transurethral prostatectomy an even safer procedure

North End of Front Street San Diego 3 Calif

Although a patient with a cardiovascular problem may present a poor surgical risk, it is felt that these patients have more resiliency than was once thought Perhaps more of the "prohibitive risk" patients, in the hands of well-trained resectionists, using isotonic solutions, can be offered a more comfortable life

The results of this study show that certain precautions are necessary in the transurethral method of prostatectomy and that these must be observed if distressing, even disastrous, complications are to be avoided Since we are unable to correlate the amount of fluid absorbed, with any degree of accuracy, with the nature of the resected prostate, it seems wise that all patients who are to undergo transurethral prostatectomy should be given the benefit of such precautions

(1) Patient should be moderately dehydrated, especially if he presents a cardiac problem

(2) Intravenous fluids should be kept to a minimum Give only enough to prevent the needle plugging

(3) Preoperative antibiotics are helpful in avoiding chills and fever postoperatively

(4) Should bradycardia, progressive blood pressure rise, or agitation of the patient develop during a resection, the procedure should be terminated as quickly as possible by fulgurating arterial bleeders and inserting a hemostatic bag

(5) Should signs of intravascular infusion develop, the patient must be watched closely after operation for instability and sudden collapse of the cardiovascular system Measures for correction should be at hand, i e , whole blood, oxygen, and vasopressor drugs to avoid shock and thus prevent oliguria[11]

(6) The use of an isotonic irrigating solution is mandatory

(7) An optimum height of the irrigating fluid source was found to be 28 inches above the bladder

(8) The anesthetist should be aware of the danger of intravascular infusion and should watch the patient closely for signs of the occurrence

(9) Excessive intravesical pressure should be avoided, especially during the latter phase of the prostatectomy

(10) Avoid cutting too close to the capsule in one area early in the procedure

(11) Avoid sinuses by stopping the resection depth when coarse circular fibers of false capsule are exposed Do not expose the fine, hard, glistening, circular fibers of the true capsule

CONCLUSIONS

(1) Volumetric, gravimetric, and radioisotopic measurements of intravascular infusion of irrigating solution correlate closely

(2) Direct measurement of radioactive irrigating fluid is relatively accurate and simple

(3) I^{131} tagging of irrigating solution is safe and accurate, and may be adjusted so that one count per minute indicates 1 cc of absorption

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[11] Bunge, R G and Barer A P Hemolysis during transurethral prostatic resection J Urol *60* *122* *1948*

- b Too high level of spinal anesthesia
- c Possible toxic action of glycine
- d Adrenal insufficiency

B Cases with initial rise in blood pressure

- 1 Dilutional or hyponatremic shock

Perforation With the classical syndrome of perforation, we are all unfortunately familiar With everything going nicely and usually with the resection approaching the capsule, the patient suddenly complains of acute pain in the lower abdomen, accompanied by a marked drop in blood pressure, pallor, perspiration, and other signs of vascular collapse

RELATION OF TYPE OF IRRIGATING FLUID TO SHOCK AFTER EXTRAVASATION

Perforation does not lead to severe shock if an isotonic irrigating solution is used If distilled water is used, however, perforation leads to great pain, even with anesthesia, and an immediate drop in blood pressure An episode of marked hypotension during transurethral resection contributes to the causation of acute renal failure, even when the renal failure is primarily due to incompatible transfusion or intravascular hemolysis from irrigating fluid entering the circulation It has been argued that with an isotonic irrigating fluid the operator may not know when he has perforated This is true and is an obvious disadvantage A perforation of consequence, however, will diminish or abolish the return of irrigating fluid, and will hardly be missed by the alert operator, and even with isotonic irrigating fluid some pain may be felt

The recognition of irrigating fluid entering the circulation as a cause of postoperative transurethral reactions was due to the observations of McLaughlin, Foley, Emmett, and Creevy Ebert was the first to suggest isotonic irrigants as a solution to the problem He first recommended glucose, but because of stickiness and poor visibility later changed to 1 8 per cent urea, subsequently reducing this to 9 per cent urea Credle, Warren and Vest then contended that urea solutions were just as hemolytic in the bloodstream as distilled water, and favored glycine, which was first advocated by Nesbit The failure of urea solutions to prevent hemolysis has since been abundantly confirmed

Distilled water may contribute to morbidity and mortality in three distinct ways 1) severe shock and blood pressure drop if extravasation occurs, 2) by causing intravascular hemolysis, and 3) by the low salt syndrome The first two of these disadvantages are overcome by the isotonic solutions such as glycine and the sugars, but the disadvantage of poor vision is added, and the low salt syndrome still occurs

That the adoption of isotonic irrigating solutions has not been by any means universal, in spite of the well publicized dangers inherent in the use of water, is an eloquent testimony to the value many of the busiest resectionists place on clear vision

Urea solutions possess the property of preventing shock on extravasation to a large degree but intravascular hemolysis still takes place Vision, however, is essentially as good as with distilled water In addition, urea solutions are com-

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TYPES OF SHOCK-LIKE REACTION DURING TRANSURETHRAL RESECTION AND RELATION TO ACUTE RENAL FAILURE

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Further reduction of the commendable mortality of transurethral resection requires an examination of some of the rare complications, and the conquest, if possible, of two of our remaining problems, the various forms of shock occurring during or just following transurethral resection, and the problem of acute renal failure These two complications may or may not be related in the individual case

The understanding of untoward reactions occurring during or just after transurethral resection has recently been greatly clarified by the identification of a certain group of these reactions with the low salt syndrome, familiar to internists for some time

Hagstrom first suggested low serum sodium as a cause of certain reactions, and stated that this explanation was suggested to him by Moyer

Harrison and associates later in an excellent analysis suggested the term dilutional hyponatremic shock

The purpose of the present study is to further evaluate the low salt syndrome, and to correlate its treatment with other factors in the prevention of acute renal failure

MATERIAL AND METHODS

The material for this study consisted of a series of 26 cases at the Veterans Administration Hospital, San Francisco, in which pre- and postoperative electrolyte studies were done, and a second series of 12 cases from private practice in which urea solution was used as the irrigating fluid In this series pre- and postoperative sodium and urea estimations were done Two case histories of severe hyponatremic shock are appended

CLASSIFICATION OF TYPES OF ACUTE REACTION FOLLOWING TRANSURETHRAL RESECTION

The types of untoward reactions occurring during or immediately following transurethral resection may profitably be classified as to whether the blood pressure is raised or lowered

A Cases with an immediate fall in blood pressure
  1 Sudden shock and vascular collapse with pain
    a Perforation and extravasation
    b Cardiovascular accidents, coronary embolism, etc
  2 Gradual shock, usually without pain
    a Excessive blood loss

Read at annual meeting of Western Section of American Urological Association Seattle, Wash May 27-30, 1957

TABLE 1 *Sodium drop blood pressure rise and hemoglobinemia in 14 cases showing significant changes*

Na		Blood Pressure Rise mm. Hg.	Hemolysis in Serum mg. %
Drop	mEq		
1	9	36	136
2	14	20	520
3		60	455
4	2	30	5 5
5	+2	0	448
6	9	0	176
7		50	5 6
8	6	−20	180
9		30	6
10	3	−2	257
11	7	10	190
12	7	58	740
13	6†	30	*100—
14	15‡	0	*300—

Cases 1 to 12 received 500 cc 11 per cent sodium chloride during surgery or 55 gm sodium chloride

* Hb estimated About 75 mg per cent just visible

† Postoperative three hours sodium has dropped further

‡ Postoperative sodium 120 preoperative not done

80 Operation lasted 45 minutes during which time blood pressure rose to 190 at the close continuing to rise to a peak of 205 ninety minutes after surgery Patient vomited, was irrational, exhibited twitchings and looked very sick. Blood pressure then steadily dropped to 118 systolic four hours postoperatively Patient continued to show irrationality, twitchings, nausea and vomiting Eight hours postoperatively the diagnosis of low salt syndrome was made The sodium determination at this time was 121 m Eq and the chloride 90 m/Eq Sodium chloride intravenously (3 per cent, 500 cc) caused prompt improvement after which patient slowly recovered over the next 24 hours

Case 2 L.A aged 75 years, underwent transurethral resection 50 minutes duration The systolic pressure remained at 120 throughout, but at close suddenly began to rise to a peak of 180 only 20 minutes after close of operation Patient exhibited restlessness, disorientation nausea and vomiting and seemed to be the exact duplicate of the foregoing case Profiting by the previous experience 500 cc 3 per cent sodium chloride was started 45 minutes after surgery, with immediate recovery

Serum showed marked hemolysis in both cases Pre- and postoperative sodium levels are not available for case 2

A study of table 1 indicates that mild degrees of the low salt syndrome as suggested by a sodium drop and a blood pressure rise occurred in 27 per cent of our cases pletely nontoxic In fact, glycine is detoxified if converted into urea, but if the other metabolic pathway into ammonia takes place, toxic reactions may occur

Other well-known causes of shock with hypotension are spinal anesthesia, adrenal failure, excessive blood loss, and cardiovascular accidents

TOXICITY OF GLYCINE

During the last few years it has been recognized that glycine is a potentially toxic substance and can cause shock, vomiting, cardiac arrhythmia, and even death The question immediately arises as to whether some of the transurethral resection reactions in which glycine was used as the irrigating fluid could have been caused by the toxicity of glycine

A study of the toxic dosage in animals indicates that this is a possibility According to Handler, Kamm, and Harris, an intravenous dose of glycine greater than 421 mg of amino nitrogen per kilogram per minute is invariably fatal to dogs If one liter of 1 1 per cent glycine were to enter the circulation in 60 minutes, in a 70 kg man, the dose would be 5 5 mg per kg /min Even so, Harold Harper states

"I do feel, however, that if glycine is otherwise satisfactory, there is no metabolic contraindication to its use *It is customary to use amino-acid* mixtures in 5–6 per cent concentrations for intravenous administration without concern if given over about a 3 hour period for 1 liter infusion I rather doubt that even if as much as 2 liters of a 1 1 per cent solution of glycine enters the circulation there would by any serious toxic effect from ammonia or other metabolic products provided the total infusion extended over a 2 hour period If the patient had considerable impairment of liver function, perhaps this might not be so but ordinarily I think this amount of the amino-acid could be handled "

DILUTIONAL HYPONATREMIC SHOCK

The recognition of a certain group of transurethral shock reactions as instances of the low salt syndrome marks a great advance

Little need be added to the description of Harrison and associates "An increasing blood pressure, slow pulse, apprehension, nausea and vomiting, twitching, irrationality, shortness of breath, cynanosis, convulsions and coma oliguria or anuria may follow " Although the blood pressure is initially raised *toward the end of the transurethral resection* due to hypervolemia, peripheral vascular collapse may later follow if the hyponatremia is not corrected Under these circumstances we would have the two main requisites for the development of acute renal failure fulfilled, i e , intravascular hemolysis and a period of marked hypotension Hagstrom reported some cases dying in the stage of coma

Our experience to date has served to confirm the essential features of this syndrome

CASE REPORTS

Case 1 J.A , aged 72 years, *underwent transurethral resection* Preoperative sodium determination not done Operation began with blood pressure of 140/

TABLE 1 *Sodium drop, blood pressure rise and hemoglobinemia in 14 cases showing significant changes*

Na		Blood Pressure Rise mm Hg	Hemoglobin in Serum mg %
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ACUTE RENAL FAILURE (LOWER NEPHRON NEPHROSIS)

A tremendous amount of clinical and experimental work has been done to elucidate the exact causes of this syndrome, and a detailed discussion is beyond the scope of this paper

A summary of recent opinion, however, would seem to be that a period of anoxia of the renal tubular cells, plus the presence of hemoglobin, are the usual causative factors Since incompatible transfusion, even with normal kidneys, can cause the syndrome, it is apparent that anoxia from surgical shock or other cause is not always necessary Since crystalline hemoglobin alone does not cause the syndrome, the possibility of the stroma of the red cells being a factor has been suggested

Following transurethral surgery, however, both anoxia and hemoglobinemia are usually present in those cases showing severe reactions

DISCUSSION

There seems to be an irreducible minimum of cases showing entry of irrigating fluid into the circulation during transurethral resection The suggestion of Griffin to leave areas in which venous sinuses are most apt to be entered until the last, or not resect them at all, should be universally followed

Whereas dilutional hyponatremia may cause distressing symptoms during the initial stages when hypertension is present its real threat to mortality lies in the period of marked hypotension which follows if the sodium deficit is not promptly corrected

This period of hypotension, added to hemoglobinemia, may lead to acute renal failure

Recognition of the signs and symptoms of the low salt syndrome, making possible its correction before the stage of hypotension is reached, constitutes a great advance

A rough estimate of the sodium deficit can be arrived at by the following considerations If 2 liters of water without sodium were added to the circulation there would be a sodium chloride deficit of 18 gm , or enough to cause a definite low salt syndrome Hence, if one liter of irrigating fluid enters the circulation, and one liter of 5 per cent glucose in water is given intravenously during the surgery, the syndrome of hyponatremia may be produced

Conversely, if the intravenous solutions given during surgery were in the form of isotonic sodium chloride, it would seem that the incidence of the low salt syndrome would be greatly reduced

Harrison and associates have proposed a definite formula for computing the sodium deficit, but the formula requires knowledge of the amount of irrigating fluid entering the system Since this varies widely, from 10-30 cc per minute of operating time according to Hagstrom, a rough estimation is all that is possible In his studies, Hagstrom obtained a fairly accurate figure by weighing patients before and after surgery

Data supplied by Landsteiner and Finch are also helpful in estimating the amount of fluid entering the circulation In one case of hemoglobinemia, they tagged the irrigating fluid with salicylate, and estimated that 1000 cc entered the circulation

In another experiment, they gave distilled water intravenously to human subjects, and found hemoglobin in the serum varying from 11 mg per cent with 100 cc water to 380 mg per cent with 900 cc water

It is significant that in no case did reaction develop nor signs of kidney damage

In the experience of those who irrigate with water, a serum hemoglobin of 300–400 mg per cent is not too rare and in one case of our series a level of over 700 mg per cent was found

Goodwin, Cason and Scott in an analysis of 69 cases found two cases of 400, two over 600, and one case of 875 mg per cent of hemoglobin in the serum

From these considerations it would seem that fluid entry would range from 1000 cc to 2000 cc in cases exhibiting mild to pronounced dilutional hyponatremia, and that the sodium chloride deficit would be 9–20 gm, rarely more

The case of Harrison and associates had vomiting, visual disturbances, and cyanosis with subsequent vascular collapse and blood pressure of 80/40 This pronounced case was estimated to have a sodium deficit of 16 5 gm, or as expressed as sodium chloride, approximately 40 gm

Diuresis during the period of hemoglobinemia is probably a definite factor in preventing acute renal failure, as indicated by Credle, Warren and Yest

In order to insure diuresis, it would seem best to give glucose in hypertonic solution, since there is already an excess of water in the blood A normally functioning kidney will tend to conserve the sodium and let the water go through

CONCLUSIONS

The low salt syndrome or dilutional hyponatremia occurred in a mild form in approximately 30 per cent of a series of transurethral resections

Case reports of two severe reactions are presented

Preoperative estimation of serum sodium is recommended If low and associated with low blood pressure, more refined tests for possible adrenal insufficiency should be done

If a general rise in systolic pressure occurs during, toward the close of, or immediately after a resection, accompanied by restlessness, mental confusion, headache nausea and vomiting, and in severe cases cyanosis and even coma, a low salt syndrome may be diagnosed Serum sodium should be estimated, and 5 per cent sodium chloride started at once, giving amounts ranging from 100 cc to 500 cc, depending on whether reaction is mild, medium, or severe Early treatment will prevent the hypotensive phase, and thus aid in prophylaxis of acute renal failure

A serum sodium level of 120 m/Eq is approximately the borderline between mild and severe reactions

Since the low salt syndrome following resection is due to entrance of excess water, a minimum of water should be given intravenously during surgery, and that in the form of isotonic sodium chloride, or Ringer's solution

Possible toxic action of glycine should be considered in reactions exhibiting nausea, vomiting, shock, and even coma Since glycine exerts toxicity by conversion into ammonia, study of blood ammonia levels in the future will be advisable in cases showing these symptoms, until the question of glycine being a factor in reactions is definitely settled

A large number of resections are still being done using water as an irrigating solution This includes some of our larger clinics, and most experienced resectionists

Obviously clear vision is considered by this group as more essential than prevention of hemolysis It is suggested that this group use 8 per cent urea instead of water

Urea gives clear vision and has the advantage over water of preventing blood pressure drop on extravasation It is completely nontoxic As is well known, it has no value in preventing hemolysis

The practice of starting the resection with 8 per cent urea, and switching to one of the nonhemolytic solutions for a short time if venous sinuses are entered, has much to commend it for use by the apparently large group of resectionists who feel that poor vision may be a greater hazard than hemolysis

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STUDIES IN THE PREVENTION OF FIBRINOLYSIS OCCURRING IN PROSTATIC SURGERY

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The many clinical reports in recent years of abnormal bleeding during and following prostatic surgery have stimulated investigation in the pathogenesis and treatment of fibrinolysis The occurrence of this hemorrhagic diathesis in nonoperative cases with metastatic cancer of the prostate has been reported by Tagnon and his associates[1] [2] Because of the rarity of this complication it is only recently that the true evaluation of hypofibrinogenemia has been brought to the attention of clinicians

CASE REPORTS

The following brief case reports of hypofibrinogenemia illustrate the varied circumstances under which fibrinolysis may occur

Case 1 J L , a 58-year-old white man, was brought to our hospital because of inability to urinate He gave a history of symptoms of progressive urinary obstruction for six months Two days before admission black tarry stools were noted On rectal examination the prostate was two times enlarged and clinically malignant A catheter was passed and the bladder aspirated of grossly bloody urine and clots The blood clotting time was normal, but complete clot lysis occurred in one hour The plasma fibrinogen level was 100 mg per cent, the prothrombin time 70 per cent and the serum acid phosphatase 34 King-Armstrong units The laboratory findings, the profuse urethral bleeding, melena, and the observation of blood oozing from the site of fresh punctures in the skin establish the diagnosis of fibrinolysis

This case illustrates that surgery, medications and blood transfusions were not the precipitating factors in the lytic process

Case 2 J B , an 83-year-old white man, entered the hospital with complaints of back pain, weight loss, and urinary frequency On rectal examination the prostate was enlarged and clinically malignant The blood hemoglobin was 12 gm , the urea nitrogen 41 mg per cent, the serum acid phosphatase 4 King-Armstrong units X-ray of the chest and abdomen revealed no evidence of metastases Cystourethroscopy and biopsy with a Silverman needle were performed as part of the diagnostic workup The prostatic biopsy proved to be adenocarcinoma One hour following cystoscopy, profuse urethral bleeding developed The blood clotting level at this time was 5 minutes with complete lysis of the clot in four hours The prothrombin time was 90 per cent and the fibrinogen level 90 mg

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Read at annual meeting of Western Section of American Urological Association May 27–30 1957

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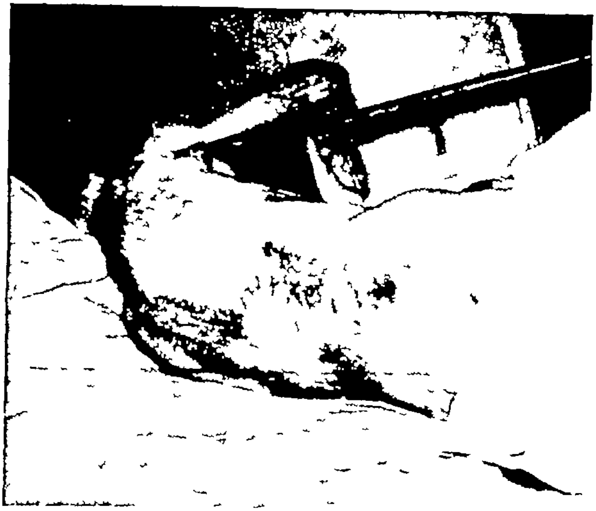

FIG 1 Case 2 Note subcutaneous ecchymoses during fibrinolysis

per cent Figure 1, a photograph of the patient's back six hours after the onset of the urethral hemorrhage, shows subcutaneous ecchymoses

Again operation, medications, and blood transfusions cannot be incriminated as etiologic factors

Case 3 J D , a 49-year-old white man, was admitted to the hospital because of severe urethral bleeding He presented a long history of chronic cystitis and prostatitis Tuberculosis as an etiological factor had been eliminated on several occasions by culture and guinea pig inoculation of the urine A right nephrectomy had been performed 16 months prior to admission for a calculous pyonephrosis X-rays of the chest, abdomen and pelvis six months preceding admission were negative for metastatic disease On admission a plain x-ray of the abdomen revealed generalized and extensive osteoblastic and osteolytic metastases to all bones The blood hemoglobin was 4 gm , the A/G ratio 2 1/2 0, the prothrombin time 90 per cent and the fibrinogen level 50 mg per cent The clotting time was 5 minutes with partial lysis in one hour and complete lysis in 20 hours The impression of chronic cystitis gleaned from repeated cystoscopies was confirmed by bladder biopsies Three weeks following admission the patient succumbed and autopsy revealed epidermoid carcinoma of the bladder with extensive metastases

Fibrinolysis in patients with metastatic cancer of the prostate is now established This case is presented to point out the varied conditions in which this disease occurs in urological practice

Case 4 H P , a 67-year-old white man, entered the hospital because of back pain and symptoms of urinary obstruction On examination he had a clinically malignant carcinoma of the prostate A plain x-ray of the abdomen showed extensive bony metastases The serum acid phosphatase was 33 2 King-Armstrong units The urea nitrogen, serum albumin and serum globulin and icterus index were normal The blood hemoglobin was 11 5 gm and the clotting time five minutes The clot showed partial lysis in 30 minutes The prothrombin time was 70 per cent and the fibrinogen level 180 mg per cent

This case illustrates the need to be alert to this proteolytic diathesis If transurethral prostatic surgery or orchiectomy were undertaken without correction or control of the lytic process, severe postoperative bleeding could develop

IN VIVO STUDIES

A complete review of the current concepts of the proteolytic enzyme systems is not possible in this paper Unfortunately the terminology for these lytic processes is not standardized A balanced enzyme system exists in plasma with delicate equilibrium between an active enzyme called plasmin and its inhibitor called antiplasmin The precursor of plasmin is termed plasminogen An imbalance of this enzyme system may occur in pathological conditions resulting in severe bleeding manifestations Investigators have shown that this system may be activated by a number of agents including body tissues Prostatic tissue, which is most pertinent to this discussion, is also an activator This is easily demonstrated by the fibrin plate method of Permin[3] In this method a fibrin plate is prepared in a sterile Petri dish by mixing fibrinogen solution and a buffer and coagulating the solution with thrombin Tissue fragments and extractions of ground tissue of benign prostatic hyperplasia and prostatic carcinoma were placed on the fibrin plates After incubation for 12 hours at 39C a dissolved fibrin zone is noted surrounding the tissue fragment or extract The zone is greatest in carcinoma of the prostate For interpretation of this we must know that in the fibrin plate there is present plasminogen or prolysin, the precursor of the plasmin enzyme system In the preparation of fibrinogen, plasminogen is a contaminate, because no procedure is available which will produce fibrinogen free from plasminogen We infer from this first step that in prostatic tissue there are activators of the plasma proteolytic system Lassen[4] has shown that the plasminogen or prolysin can be destroyed by heat denaturation at 80C for 30 minutes This makes the fibrin plate insensitive to fibrinolytic activators while the sensitivity towards fibrinolytic enzymes is largely retained A heat denatured fibrin plate with a pure activator such as streptokinase placed on its surface will show no zone of dissolution because no lytic enzyme precursors are available for activation Tissue fragments and extractions of benign and malignant prostatic tissue placed on denaturated fibrin plates give zones of fibrin dissolution We conclude from this demonstration that prostatic tissue contains in addition to activators of the plasma enzyme system a fibrinolytic system of its own

The actual cause of proteolysis associated with prostatic surgery is unknown The process may be entirely due to the intravascular release of the prostatic proteolytic enzyme or may be due to intravascular release of enzyme activators from the prostate triggering the plasmin system

The next step in our study of proteolytic enzymes was to find effective inhibi-

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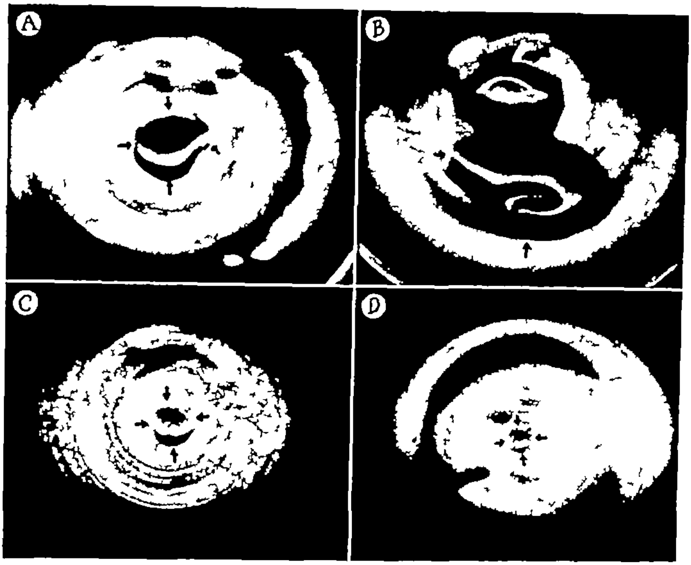

FIG 2 *A*, heat denatured fibrin plate incubated with extract of benign prostatic tissue shows zone of lysis *B*, heat denatured fibrin plate incubated with extract of malignant prostatic tissue shows large zone of lysis *C*, heat denatured fibrin plate prepared with toluidin blue and incubated with malignant prostatic tissue shows inhibition of lysis *D*, heat denatured fibrin plate prepared with klot and incubated with malignant prostatic tissue shows inhibition of lysis

tors Two products have been evaluated in this study, toluidine blue* and klot † Toluidine blue (3 amino-7-dimethyl-amino-2-methylphenazatheonium) has been found to counteract bleeding in a wide variety of hemorrhagic states with disturbances of the blood clotting mechanism secondary to the presence of a heparin-like anticoagulator Klot is an aqueous solution of 7 per cent n-butyl alcohol and 0 002 per cent toluidine blue in a normal saline vehicle From our in vitro studies we have found this concentration of toluidine blue to be ineffectual as an inhibitor but a number of clinical studies have shown the hemostatic effect of n-butyl alcohol[5] [6]

Preliminary in vitro studies showed that both these agents, toluidine blue and klot, were effective inhibitors of the prostatic fibrinolysin As mentioned above an extract of benign prostatic tissue on a denatured fibrin plate incubated for 12 hours showed a zone of fibrin dissolution Figure 2, *A* is a photograph of such a plate Figure 2, *B* is a fibrin plate on which an extract of malignant prostatic tissue was placed and allowed to incubate 12 hours Note the much larger zone of liquefaction occurring in carcinoma of the prostate

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* Supplied through the courtesy of Abbott Laboratories

† Supplied through the courtesy of Mr A G Worton of the Warren Teed Products Company

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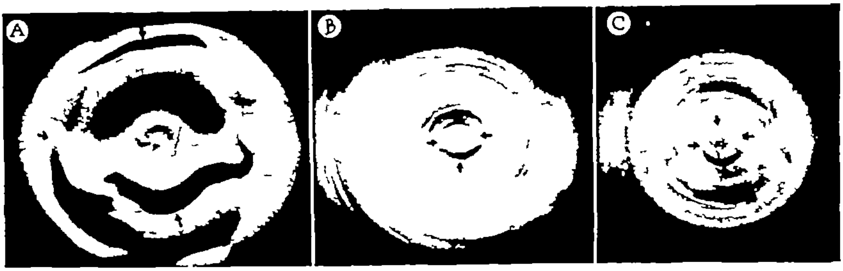


FIG 3 Case 2 *A*, heat denatured fibrin plate incubated with serum shows large zone of lysis *B*, heat denatured fibrin plate prepared with toluidine blue incubated with serum shows almost complete inhibition of lysis *C*, heat denatured fibrin plate prepared with klot incubation with serum shows almost complete inhibition of lysis

In figure 2, *C* the fibrin plate was prepared with the addition of toluidine blue The same extract of malignant prostatic tissue used in figure 2, *B* was placed on the plate and incubated The zone of dissolution is much decreased indicating almost total inhibition Similarly, in figure 2, *D*, a fibrin plate with klot was prepared and the same extract of malignant prostatic tissue incubated Again almost total inhibition of lysis is noted

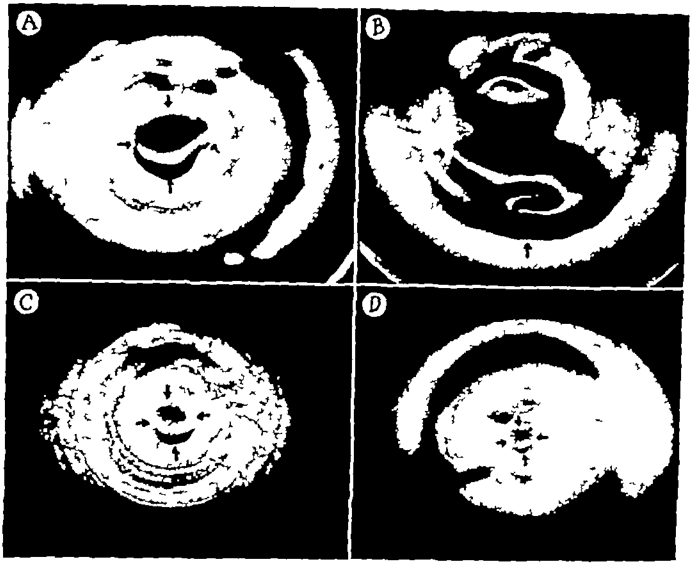
The serum of case 2, taken during the acute fibrinolytic period, was placed on a fibrin plate and incubated Figure 3, *A* shows the very large area of dissolution Figure 3, *B* and *C* respectively are plates showing inhibition by toluidine blue and klot

CLINICAL STUDY TOLUIDINE BLUE AND KLOT, EFFECTS ON PLASMA FIBRINOGEN LEVELS

From the results of the in vitro studies a clinical survey was undertaken to evaluate the antifibrinolytic effects of toluidine blue and klot In this study fibrinolytic activity was adjudged by plasma fibrinogen determinations rather than other more complex and expensive determinations of lytic activity There is a wide range of variation in the plasma fibrinogen from the accepted normal level of 250 to 350 mg per cent Rarely is a level found below the low of normal, however, many levels are found above the high of normal Infections and inflammatory processes are the most common causes of elevated plasma fibrinogen levels

Plasma fibrinogen was determined preoperatively, one hour and four hours postoperatively in three groups of 30 consecutive transurethral prostatectomies The first group, the controls, received no special medications and fibrinogen determinations were done at the intervals stated The second group received 200 mg blutene, an oral toluidine blue preparation, 12 hours before surgery The third group was given klot intravenously at the start of resection in a dosage of 1 cc per 15 pounds of body weight

In the control group the average drop in fibrinogen from a comparison of the preoperative and the four hour postoperative fibrinogen was 20 3 per cent Simi-



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* Supplied through the courtesy of Abbott Laboratories

† Supplied through the courtesy of Mr A G Worton of the Warren Teed Products Company

[5] Revici, Emanuel and Ravich, R A Antihemorrhagic action of n butanol in advanced cancer Angiology, 4 510 1953

[6] Ravich, R A and Ravich, A Clinical application in urological surgery of a new concept of physico chemistry of pathological lesions J Urol , 62 629, 1949

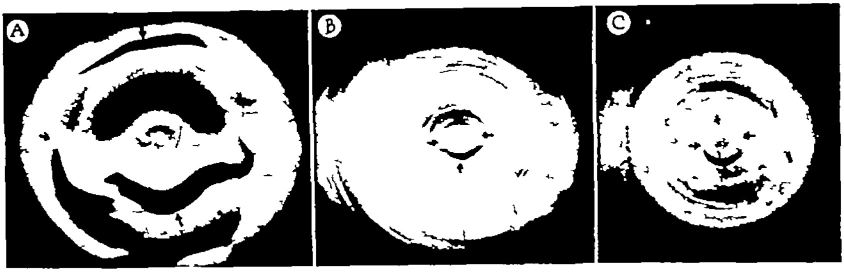

FIG 3 Case 2 *A*, heat denatured fibrin plate incubated with serum shows large zone of lysis *B*, heat denatured fibrin plate prepared with toluidine blue incubated with serum shows almost complete inhibition of lysis *C*, heat denatured fibrin plate prepared with klot incubation with serum shows almost complete inhibition of lysis

In figure 2, *C* the fibrin plate was prepared with the addition of toluidine blue The same extract of malignant prostatic tissue used in figure 2, *B* was placed on the plate and incubated The zone of dissolution is much decreased indicating almost total inhibition Similarly, in figure 2, *D*, a fibrin plate with klot was prepared and the same extract of malignant prostatic tissue incubated Again almost total inhibition of lysis is noted

The serum of case 2, taken during the acute fibrinolytic period, was placed on a fibrin plate and incubated Figure 3, *A* shows the very large area of dissolution Figure 3, *B* and *C* respectively are plates showing inhibition by toluidine blue and klot

CLINICAL STUDY TOLUIDINE BLUE AND KLOT, EFFECTS ON PLASMA FIBRINOGEN LEVELS

From the results of the in vitro studies a clinical survey was undertaken to evaluate the antifibrinolytic effects of toluidine blue and klot In this study fibrinolytic activity was adjudged by plasma fibrinogen determinations rather than other more complex and expensive determinations of lytic activity There is a wide range of variation in the plasma fibrinogen from the accepted normal level of 250 to 350 mg per cent Rarely is a level found below the low of normal, however, many levels are found above the high of normal Infections and inflammatory processes are the most common causes of elevated plasma fibrinogen levels

Plasma fibrinogen was determined preoperatively, one hour and four hours postoperatively in three groups of 30 consecutive transurethral prostatectomies The first group, the controls, received no special medications and fibrinogen determinations were done at the intervals stated The second group received 200 mg blutene, an oral toluidine blue preparation, 12 hours before surgery The third group was given klot intravenously at the start of resection in a dosage of 1 cc per 15 pounds of body weight

In the control group the average drop in fibrinogen from a comparison of the preoperative and the four hour postoperative fibrinogen was 20 3 per cent Similarly the drop in the toluidine blue group was 11 0 per cent and in the klot group 6 3 per cent

Interesting also is the observation that in six of the 30 in the control group the fibrinogen dropped below the low of accepted normal, 250 mg per cent, in the fourth postoperative hour One of the six dropped to zero or afibrinogenemia In the groups treated with toluidine blue and klot none of the fibrinogen determinations four hours postoperatively were below normal In seven of the group treated with klot the four-hour fibrinogen was elevated above the preoperative fibrinogen

DISCUSSION

The exact details of the mechanism of abnormal proteolytic activity are as yet undermined The problem of fibrinolysis assumes greater significance as illustrated in the case reports of this paper It can occur in patients who have not undergone operation In an earlier paper we reported fibrinolysis occurring in five cases following transurethral surgery [7] In our experience we have encountered fibrinolysis with severe systemic manifestations following suprapubic enucleation of a benign adenoma

It appears that fibrinolysis occurs primarily in those cases in which venous sinuses are entered Open venous sinuses certainly are a mode of entry of enzyme activators or enzymes into the circulation Fibrinogen determinations were done preoperatively and postoperatively as in other studies on men undergoing transurethral resection of bladder tumors The plasma fibrinogen levels in these cases remained constant throughout A possible deduction from this is that manipulation or massage of the prostate by a sheath riding over the prostate is not sufficient for intravascular release of prostatic proteolytic activators or enzymes It is logical in our search for etiologic factors to consider irrigating solutions

The proteolytic inhibitors, toluidine blue and klot, have been demonstrated to be effective in the prophylactic prevention of fibrinolysis We have effectively treated the proteolytic diathesis in postoperative hemorrhage with klot and whole blood alone Important in the treatment is early recognition Whole blood is administered to replace blood loss and maintain blood volume and to supply substrate for the enzyme Klot is given intravenously, 1 cc per 10 pounds of body weight Repeat dosages of klot are given at two-hour intervals depending on the severity of the hemorrhage If the plasma fibrinogen is below normal, 250 mg per cent, human fibrinogen is also administered Multiple 1 gm doses are given intravenously until there is lessening of bleeding The total amount of fibrinogen generally used is from three to six grams

This method of treatment should not be interpreted as a substitute for good hemostasis by the operator at the time of surgery We have been able to reverse effectively a previously grave prognosis in this complication of transurethral prostatectomy

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[7] Lombardo, L J Fibrinolysis following prostatic surgery J Urol , 77 289, 1957

SUMMARY

Brief case reports of hypofibrinogenemia are presented in nonoperative cases

The in vitro and in vivo studies of the proteolytic inhibitors, toluidine blue and Klot, are presented

Recommendations are made for the treatment of fibrinolysis occurring following prostatic surgery

I wish to thank Dr Hans Zinsser who stimulated my interest in this problem and Mr Jack Kortzeborn for his laboratory assistance

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UROLOGIC COMPLICATIONS OF IMPERFORATE ANUS

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Congenital malformations of the anus and rectum are frequently encountered in neonatal life Incidence of such anomalies has been variously reported at from 1 in 1,500 to 5,000 births The urgent nature of these malformations is unquestioned Less well appreciated, however, is the frequency and gravity of coexistent anomalies of the genitourinary system While these lesions may be perfectly obvious at birth, more often their presence is neither suspected nor ultimately identified until the best opportunity for management has passed The death of children suffering imperforate anus several years after satisfactory management of the alimentary lesion is often due fundamentally to oversight or poor management of a urologic lesion The management of this lesion seldom requires methods dissimilar to the management of those lesions were not the imperforate anus present Certain routine urologic investigations should be carried out on all infants bearing anorectal anomaly Only in this manner may late deaths from latent urologic disease be eliminated or postponed The surgeon is indebted to Gross,[1] Berman,[2] Spence[3] and others for emphasizing these associated disorders Little sustained attention save that manifested by Spence has been directed to the multitudinous and grave nature of some of these complications Yet often the seriousness of the whole congenital monstrosity precludes successful therapy

EMBRYOLOGY

In the early development of the human embryo at 7 5 mm the urogenital sinus anteriorly has common communication with the intestinal tract posteriorly in the area known as the cloaca Cloaca is limited externally by the cloacal membrane, the membrane ultimately to give rise to the proctodeal membrane posteriorly and the urogenital membrane anteriorly By the time the embryo has reached the 9 4 mm stage the urogenital tract becomes separated from the alimentary tract posteriorly by a curtain-like fold growing caudad known as the urorectal septum Dimpling of the anal pit forming the proctodeum continues its inward growth until the proctodeum and rectum join their lumina Prior to this however the urorectal septum has completed its curtain-like division of the cloaca, bringing with it the primary excretory duct structures as they join the anterior urogenital sinus Failure of rupture of the anal membrane or development of the proctodeal dimple is held responsible for the develop-

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Read at annual meeting of North Central Section of American Urological Association, Mackinac Island, Mich , August 29–31, 1957

[1] Gross, R E Surgery of Infancy and Childhood Philadelphia W B Saunders Co , 1953, pp 348–368

[2] Berman, J K Congenital anomalies of the rectum and anus Surg Gynec & Obst , 66 11–22, 1938

[3] Spence, H M Anomalies and complications of urogenital tract associated with imperforate anus J Urol , 71 453–463, 1954

ment of imperforate anus This failure occurs during the seventh or eighth week of embryonic life Frequently coupled with this abnormality is the failure of the urorectal curtain to completely divide the anterior urogenital sinus from the posterior anal canal Thus abnormal fistulous tracts between gut posteriorly and urogenital sinus anteriorly have their inception at approximately the end of the second month of embryonic life Variation in degree of failure of the anal dimple to communicate with the hind gut gives rise to varying degrees of severity of imperforate anus Gross has classified these into four varieties for the sake of simplicity Type 1 is in truth not an imperforate anus but rather a congenital stenosis wherein a fistula communicates gut with perineum at birth The stenotic portion of the hind gut can measure as little as a few millimeters and as much as 4 cm

Type 2 A true imperforate anus is essentially no more than a membrane separating the bulging hind gut from the perineal exterior

In type 3 the rectum ends blindly at a considerable distance above the perineum

Type 4 often escapes diagnosis in the early hours of life The anus is apparently normally formed The anal canal however ends blindly from 2 to 4 cm above the anus at which point a heavy membrane between anal canal and rectum occludes

Fistulous tracts between the gut and urinary tract may exist as rectovesical or rectourethral These tracts usually occur in imperforate anus of type 3 Recto-urinary fistula in the female is exceedingly rare

INCIDENCE

One-hundred seventy-four children treated consecutively for imperforate anus at the Riley Hospital for Children constitute the basis for this report (table 1) No attempt is made in this essay to analyze complications directly attributable to the initial surgical procedure designed to relieve the anal obstruction Not only were records of early cases too inadequate to do this, but also there has been an astonishing lack of evidence of iatrogenic urinary problems in recent years Seventy-eight (45 per cent) of these children suffering imperforate anus likewise harbored genitourinary disorders Sixty were male and eighteen were female Ten of those having urologic anomalies succumbed too soon after birth to allow treatment of the urologic anomaly Of these deaths two can be attributed to urologic lesions, one, bilateral renal agenesis and the

TABLE 1 *Imperforate anus*

Consecutive cases reviewed	174
Cases with urologic complication	78 (45%)
Death prior to primary surgical intervention	10
Death after primary gut surgery	26
Urological complications not treated	16
Urological complications treated surgically	26
Total	78

TABLE 2 *Urologic complications of imperforate anus*

Fistula		49
Rectourethral	17	
Rectovesical	13	
Enterovesical	4	
Perineal	3	
Vesicovaginal (?)	1	
Rectovaginal	11	
Hydronephrosis		29
Hypoplasia (bilat)		2
Renal agenesis (unilat)		6
Double ureter		3
Ureterovesical stricture		5
Cloaca		4
Bladder "dysfunction"		18
Septate bladder		1
Patent urachus		3
Hypospadias		5
Cryptorchism		12
Genital hypoplasia		4
Exstrophia vesica		4
Urogenital sinus		2
Renal fusion		2
Urethral stricture		2
Polycystic kidney		1
Urethral agenesis		2
Prostatic agenesis		2
Agenesis of bladder		1
Agenesis of penis		1
Agenesis of testes		1
Renal ectopia		1
Ureteral triplication		1
Vesical diverticulum		1
Epispadias		1

second due to renal failure with hypoplasia of one and hydronephrosis of the opposite kidney Thus it is evident that early death from urologic complications is not an ordinary occurrence On the other hand, 26 children having urinary tract anomalies died without care of incidental urinary tract problems after major definitive intestinal surgery and other gastrointestinal lesions Sixteen children survived neonatal life with urologic problems but were never cared for in an active way Most of these were children with minor hypospadias, renal malrotation, urinary fistulous tract or other problems of urinary stasis which never came to urologic management due to their demise as a result of the gastrointestinal disorder The study herein reported is based upon 26 patients having urologic problems surviving their neonatal period and coming under the treatment of the Urology Department with definitive treatment rendered The vast majority of these children suffered urinary stasis (table 2) At least eight of those children having stasis could be attributed to neuromuscular dysfunction Often the ability to distinguish between bladder neck contracture and neurogenic dysfunction was impossible In some of the early cases studied identification of bladder neck contracture was overlooked until advanced renal damage had supervened Certainly the high incidence of bladder dysfunction in the over-all picture of urologic complications in imperforate anus is surprisingly high As far as we have been able to determine this has not been emphasized previously

DIAGNOSIS

Unquestionably the lethal characteristics of several of our cases herein studied were attributable to failure to employ routine urologic investigation early in postnatal life It has been possible for the past 5 years to investigate all newborn patients with imperforate anus within 48 hours of their birth prior to their being taken to surgery for procedures designed to relieve anal obstruction

The performance of both immediate and delayed cystograms and in some instances cinefluorographic studies have been deemed important in the workup of these patients Quite often this investigation is carried out at the time of the initial radiographic study for classification of type of anal malformation The determination of residual urine with the use of ascendant lipiodol is important Frequently intravenous urography has been valuable in establishing the early nature of the disease and provide basis for comparison in followup progress films The clinician is warned that ureterography in early neonatal life may be confusing At birth a significant amount of ureteral atony exists such that on occasion spiral valve and ureteral dilatation may be diagnosed erroneously Rectourinary fistula may be obvious at birth The passage of meconium through the penis or the identification of pneumaturia should be sufficient to identify this lesion Instillation of iodized compounds into the bladder with observation of its appearance in the rectum is proof of the intercommunication between these two hollow viscera In older patients cystoscopic and anuscopic examinations may be helpful in establishing the exact location and nature of such fistulas Reflux of cystographic medium into the upper ureteropelvic system is taken as evidence of vesical neck obstruction or neuromuscular disorder It must be mentioned however that on rare occasions it is possible for retrograde reflux to occur in the otherwise normal infant

TREATMENT

Treatment of urinary anomalies associated with imperforate anus is seldom different from the management of these lesions when unassociated with imperforate anus In relief of urinary stasis due to bladder neck obstruction or to neuromuscular dysfunction the method of management used must rest upon the degree of damage to the upper urinary tract All too often reflux discloses large hydronephrosis on one or both of the upper tracts In such instances suprapubic catheter drainage is often helpful At the time of cystostomy retropubic vesical neck resection is usually done Not infrequently cystostomy is done at the original laparotomy when anal obstruction is managed Where reflux continues to be a problem vesicoureteroplasty may be desirable Seldom in our hands is transurethral resection of the vesical neck feasible in the male infant This method has more application and usefulness in the occasional female patient suffering bladder neck obstruction Often undue delay in rehabilitation of the child is the result of purposeless preservation of functionless infected hydronephrotic sacs and their dilated tortuous ureters In such instances these useless sacs act as reservoirs for residual urine and infection Their entire removal is often followed by marked improvement in the child This is not to be construed as destructive surgery Any kidney with useful function particularly if stasis is bilateral warrants intense salvage efforts

The management of ureteral obstructions may be dealt with in the standard acceptable urosurgical methods The problem of urorectal fistula seldom falls in the province of the urologist In the hands of a careful general surgeon these fistulas will be eliminated at the time of initial repair of the imperforate anus

Occasional oversight or re-establishment of fistula makes it mandatory for the urologic surgeon to be aware of and on the lookout for such abnormal communications. In one patient in whom the rectourethral fistula penetrated the substance of the prostate gland no repair was done in the hope that the fistula would close at the time of puberal prostatic growth. This did not prove to be the case and the fistula remains to be excised. The formation of calculus in such fistulous tract is not uncommon.

The discussion of the repair of external genital abnormalities such as hypospadias and undescended testes is beyond the scope of this essay. The coexistence of imperforate anus and exstrophy of the bladder is often and in our experience incompatible with life. In the theoretical survival of such a patient it would be unwise to transplant ureters to the lower bowel in the absence of good anal control as is so often the case in these unfortunate individuals.

SUMMARY

One-hundred seventy-four children suffering imperforate anus were studied. Of these, 78 suffered associated urologic disorders, many of which were minor. On the other hand, many contributed to, if they were not entirely responsible for the patient's death. The more difficult problems of urologic complications in imperforate anus center about the coexistence of stasis and infection in the urinary tract. The unusually high incidence of vesical neck dysfunction is emphasized. Treatment of these disorders seldom differs from that of the same disorder unassociated with imperforate anus. Emphasis is placed upon early and complete urinary tract evaluation in these malformed children.

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ADENOMATOID TUMORS OF THE EPIDIDYMIS

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It has become increasingly apparent that the most common neoplasm of the epididymis is an adenomatoid one Although the term has neither genetic rectitude nor complete acceptance, it seems applicable in reference to morphologic suitability and in the resolution of much prior confusion in the terminology of epididymal tumors The earlier literature applied such terms as adenoma, lymphangioma and cystadenoma to the adenomatoid tumor It is not surprising then that prior to the review of primary epididymal tumors by Longo,[1] malignancies were considered more common Since a channeling of cases into the unified adenomatoid category has developed it is clear that benign growths account for approximately 80 per cent, and of these perhaps 75 per cent are adenomatoid

As to the derivation of this type of tumor, a mesothelial origin seems more tenable than endothelial, epithelial or mesonephric Most frequently annotated as involving the epididymis adenomatoid tumors have been found in other locations, notably the spermatic cord, tunica vaginalis and, in the female, the uterus and tubes

Regarding etiology there has been no evidence to incriminate prior infection or trauma as instigative or contributory

Clinically, adenomatoid tumors have been seen to occur at any age, but reputedly are more common in the third and fourth decades The lack of symptomatology referable to the tumor has been noteworthy Data gleaned from the largest series of cases reported[2] suggest that the globus minor is involved four times more frequently than the globus major Purportedly the tumors arise more often on the left, yet bilateral occurrence has been described[3] Slow growth has been another characteristic finding and upon examination, encapsulated separability from the epididymis and testicle Tenderness to palpation has been lacking aside from the infrequent instance of the compensation complex The tumors rather obviously are not transilluminable

The pathologic appearance of the adenomatoid tumor grossly is round, well circumscribed firm and relatively smooth The yellowish cast of the cut surface is similar to the intact appearance Histologically the pseudoacinar spaces which are characteristic are lined by a cuboidal type of cell which has in its likeness to the epithelial cell instigated misguided conjecture as to an epithelial origin (fig 1 A) The stroma is of connective tissue type and often scanty A scattering of lymphocytes is commonly associated with a focal collection of lymphocytes resembling a lymph follicle (fig 1, *B*) Smooth muscle may also be found in varying amounts throughout the stroma

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[2] Thompson G J Tumors of the spermatic cord epididymis, and testicular tunics Surg Gynec & Obst **62** 712-728 1936

[3] Morin L J Bilateral adenomatoid tumor of the epididymis J Urol 75 819-822 1956

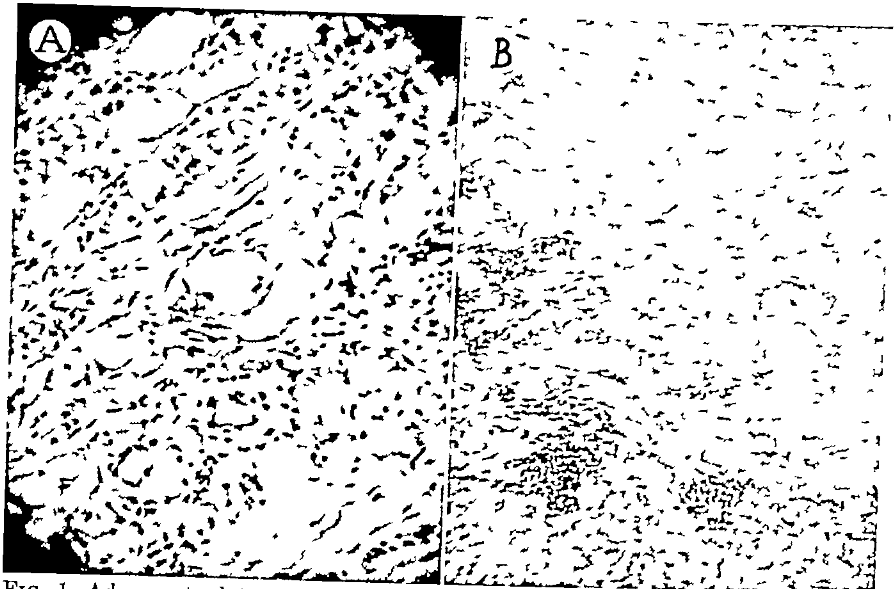

Fig 1 Adenomatoid tumor of epididymis *A*, cleft like pseudoacinar spaces visible, lined with flattened cuboidal type of cell *B*, note characteristic lymphocytic aggregates located in close proximity to pseudoacinar spaces

Data derived from five instances of adenomatoid tumor seen at the University Hospital in the past six years coincide with facts acquired from prior reports The ages of the five patients were 82, 80, 67, 52, and 39 years Three were unaware of the existence of the tumor, in the other two no symptoms had been experienced, but the presence of a mass had been noted for at least eight to ten years

Concomitant pathology was prostatic in two cases, ophthalmologic in one, and cardiovascular in two As to location, four were found to be in the region of the globus minor and one in the globus major Four of the five were discovered in the left scrotal compartment All tumors were described as firm, rounded, movable, and distinctly separable from the testis Moderate tenderness to palpation was noted in one man Surgical excision was accomplished in each instance under local anesthesia and the tumors without exception were easily enucleated from the surrounding tissue The postoperative courses of these individuals corroborate the accepted lack of recurrence or coexisting malignancy

Despite the fact that the adenomatoid tumor is becoming better known and more readily diagnosed as it becomes more widely documented, a cautionary injunction seems warranted for future peremptory dismissal of such epididymal masses as invariably benign and thus not necessitative of excision Surgical exposure should continue to be routine in view of the palpable similarity of clinical characteristics of both adenomatoid tumors and many of the lymphosarcomas and less aggressive epididymal carcinomas which have been reported

SUMMARY

The adenomatoid tumor is the most common epididymal neoplasm Five cases of these tumors are reported Despite the benignancy of the tumor, surgical excision is mandatory in view of its clinical similarity to some of the malignant neoplasms

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TORSION OF THE APPENDIX TESTIS

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There are but sporadic reports of torsion of testicular or epididymal appendages Including the four cases presented below, the total number reported to the present time is only 141 Most authors writing on the subject, however, feel that appendiceal torsion is much more frequently encountered than the paucity of reported cases would suggest If this assumption is correct, one must conclude that either seldom does the urologist trouble to report them, or that the condition is not being recognized and surgery, which would provide the correct diagnosis, is not being performed As a consequence, the condition is inaccurately finding its statistical listing as acute epididymitis, epididymo-orchitis or hydrocele

Considering this clinical entity a rare one, most texts dismiss the subject with a brief paragraph or so, merely describing the symptoms as being generally similar to those produced by torsion of the spermatic cord, though usually milder Some state that the two conditions are so similar that the correct diagnosis is more often than not made only at the operating table Such statements are misleading to the urologist who has not previously encountered appendiceal torsion because many of the cases do not even remotely resemble spermatic cord torsion, save in the history of sudden onset Thus, the surgeon, who considers the former condition only when presented with a clinical picture indistinguishable from the latter, is bound to miss the many milder, less dramatic cases of appendiceal torsion

REVIEW OF THE LITERATURE

In 1950, Seidel and Yeaw[1] reported 8 cases, bringing the total at the time to 107 cases In 1951, Bender[2] reported a case His bibliography contained three references not mentioned by Seidel and Yeaw, namely, 6 cases by Ladd and Gross and two by Coppridge and Roberts in 1941, and one by Livermore in 1948 Adding the case of Bender to the 9 cases just mentioned would bring the total to 117 In 1950 Lovell[3] reported 4 cases not referred to in any of the above reports In 1952, 2 cases were reported by Walton,[4] one by Klinger,[5] and one by Truc and associates [6] In 1953, 3 cases were reported by Hamilton and associates[7] and two by Fillis and Meyer [8] In 1956 Lowsley and Kirwin[9] mentioned a case

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[1] Seidel R S and Yeaw, R C Torsion of the appendix testis and appendix epididymis report of eight cases J Urol 63 714–716 1950

[2] Bender R I Torsion of the appendix testis A review of the literature and the presentation of a case Wisc Med J 50 670–672, 1951

[3] Lovell S H Torsion of the testis and its appendages Med J of Australia, 2 787–790 1950

[4] Walton, A J Torsion of the testis and its appendages Lancet 2 211–213 1952

[5] Klinger M E Torsion of the appendix testis N Y State J Med, 52 2040, 1952

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[7] Hamilton G R Dekovessey C A and Getz, R J Torsion of appendix epididymis and appendix testis J Urol 69 436 1953

[8] Fillis B F and Meyer W C Torsion of hydatid of Morgagni J Urol 69 836 1953

[9] Lowsley O S and Kirwin T J Clinical Urology Baltimore Williams and Wilkins Co 1956 vol 1 p 106

not previously reported, and Ambrose and Skandalakis[10] reported 6 cases Thus, to the present time, one can find 137 cases reported in journals and texts

DISCUSSION OF SIGNS AND SYMPTOMS

The early and late phases of appendiceal torsion present two entirely different clinical pictures

The early phase If the patient is seen early after the onset of symptoms there should be relatively little difficulty in establishing the correct diagnosis, if the condition is kept in mind The salient features of the early phase are as follows

1) The patient is usually an adolescent or pre-adolescent child, only 10 or so cases having been reported in the adult

2) A sudden onset of pain in the scrotum, testicle, groin, or lower abdomen, often attributed by the patient to some antecedent minimal trauma

3) The presence of varying degrees of point-tenderness in a cystic-like, pea-sized structure in the neighborhood of the upper pole of the testis (hydatid of Morgagni), or, quite rarely where the other appendages are located (organ of Giraldes and vas aberrans)

4) The presence of bluish discoloration seen through the skin overlying the twisted appendage This is readily seen in children but may be difficult or impossible to observe through the thicker scrotal skin of adults

5) The absence of tenderness in the testis, spermatic cord and the rest of the epididymal tract

6) The absence of systemic manifestations and usually the absence of significant laboratory findings

7) Prehn's sign may be positive

The late phase Following torsion secondary changes may in some cases quickly develop which will lead one to suspect spermatic cord torsion In such instances surgery will probably result and the correct answer will be obtained However, a review of various case reports reveals that in many instances there is but a slow progression of events Several days to weeks may elapse from the inception of the condition to the development of secondary changes, usually listed as epididymitis, epididymo-orchitis, or hydrocele When such changes are present palpation of the twisted appendage, the keynote to diagnosis, may be difficult or impossible However, even if the patient is not seen until this stage, as frequently happens, one should be alerted to suspect the correct diagnosis by the absence of systemic manifestations, by the history of sudden onset, by a general clinical picture out of keeping with the local findings, and by the absence of significant laboratory changes

DIAGNOSIS

A complete physical examination should be made in all cases, including rectal examination, laboratory studies, and gentle prostatic massage, with examination of any obtained secretions Hydrocele fluid, if present, may be aspirated to permit palpation of the twisted appendage The well-known gamut of differential diagnosis must, of course, always be considered

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[10] Ambrose, S S and Skandalakis, J E Torsion of appendix epididymis and testis J Urol , 77 51, 1957

TREATMENT

In general, early surgery in this condition is advocated to reduce the subsequent period of disability In a few of the reported cases, and in one reported here, non-surgical management resulted in eventual uncomplicated recovery If the assumption is true that many cases are being encountered but not recognized, it would suggest that ultimate recovery without surgery frequently takes place However, since secondary epididymitis often occurs, it is conceivable that it could give rise to subsequent unilateral obstructive sterility Also since permanent hydrocele formation may result early surgery is wisely still advocated

Since a certain latent period seems to exist in the average case between the onset of symptoms and the development of secondary complications, one need not rush into surgery in a matter of hours as one must when torsion of the testicle itself is suspected Since the appendix testis serves no useful purpose it would seem a most wise precautionary surgical measure to excise all pedunculated testicular appendages during any scrotal surgery

CASE REPORTS

Case 1 P T , aged 11 years, Alachua General Hospital No 66685, was admitted on July 10, 1953 for pain and swelling in the right testicle The pain had suddenly awakened the patient at 3 00 a.m Examination at 9 00 a.m revealed a moderately tender, pea-sized, cystic-like structure immediately adjacent to the upper pole of the right testicle Through the overlying scrotal skin a bluish discoloration was observed There was no accompanying heat, redness, or edema of the skin and no involvement of the cord structures, testicle, or epididymis Temperature, pulse, respirations, and laboratory studies were entirely normal The diagnosis was 'torsion of an hydatid of Morgagni " Over the next 24 hours treatment consisted of bed rest, scrotal elevation, ice packs and analgesics The following morning the patient was asymptomatic and he was discharged The pea-sized, cystic nodule was no longer tender No further change occurred until 4 or 5 days later, when a moderate swelling of the right scrotal structures developed Palpation then suggested moderately severe epididymo-orchitis There was, however, surprisingly little tenderness There was no fever or systemic manifestations The appendix testis could no longer be distinguished on palpation Further supportive therapy was carried out and over the course of the next two weeks the swelling gradually subsided with ultimate total recovery without known sequellae

Case 2 C M , aged 16 years, Alachua General Hospital No 80703, was admitted on November 12, 1955, for sudden severe pain and swelling of the left testicle At approximately 4 00 p m the patient experienced a sudden onset of moderate pain in the left testicle, which was not accompanied by any swelling The testicle, on self-palpation, revealed only mild tenderness at one point It was quite similar to two or three previous attacks the patient had had over the past 2 or 3 years He was, therefore, not alarmed because spontaneous remissions usually quickly followed About six hours later, a sudden, very severe pain was noted, followed in a matter of 15 minutes by rapid swelling of the left scrotal contents Examination approximately *one hour later revealed the left hemiscrotum* to be two or three times normal size with exquisite tenderness on any attempted palpation Prehn's sign was positive The patient appeared acutely ill The preoperative diagnosis was "torsion of the left testicle" At surgery, performed within the ensuing hour, three complete turns of the spermatic cord *in a clockwise direction were found The testicle was cyanotic and all structures* below the level of torsion were quite edematous Attached to the tunica albuginea, near the globus major, was a bluish-black, twisted appendix testis This was excised, the testicular torsion was reduced, and after some five to ten minutes complete circulatory return took place Hydrocelectomy and orchiopexy were *performed A prophylactic* orchiopexy and excision of the appendix testis were performed on the opposite side Convalescence was uneventful, the patient being discharged on his seventh postoperative day On a six-month checkup both testicles appeared entirely normal on palpation

Case 3 F H, aged 10 years, Alachua General Hospital No 83810, was admitted on *May 7, 1956* for surgery with a preoperative diagnosis of "acute right hydrocele, secondary to torsion of the appendix testis" Early the morning of April 26, 1956, the patient had noted the sudden onset of right testicular pain with right lower quadrant and epigastric radiation The pain was not severe but sufficient malaise and discomfort were present to make him request that he be permitted to stay home from school Vague lower abdominal and right scrotal discomfort continued until the patient was seen in urological consultation the following day The only positive physical finding was the presence of a mildly tender, pea-sized nodule adjacent to the upper pole of the testis The scrotal contents were otherwise normal A bluish discoloration could be noted through the skin overlying the appendage Non-surgical treatment was recommended since the physical findings appeared so insignificant The mother was apprised of the diagnosis of torsion of the appendix testis and that possibly subsequent surgery might be necessary depending upon the clinical course The mother called several times over the course of the next week to report that no change in the child's condition had taken place However, on *May 6, examination revealed* that a moderately large, non-tender hydrocele had developed There were no systemic manifestations and laboratory studies were normal At surgery the following day, the hydrocele contained 20 to 25 cc clear yellow fluid The testicle and epididymis appeared normal, save for the globus major, which revealed marked vascular *engorgement together with some fibrinous* adhesions Sitting in the valley formed by the testicle on one side and the edematous ridge of the globus major on the other, was a small pea-sized structure, blackish-red in color, and attached to the tunica albuginea by a very fine twisted pedicle Excision of the hydatid and hydrocelectomy were performed The patient was discharged on the third postoperative day *Convalescence* was uneventful

Case 4 B G L, aged 10, Alachua General Hospital No 87356, was admitted on December 12, 1956 Pain and swelling in the left testicle were the presenting complaints Four days previously he had received a blow to the left testicle while playing football Some pain was noted for perhaps five minutes after injury, but he was then unaware of any further difficulty for the next two days On the third day dull aching in the left scrotum began and during the course of the day progressive swelling of the left hemiscrotum occurred There were no associated urinary symptoms, abdominal complaints, fever, or history of previous similar episodes Examination revealed an enlarged left hemi-scrotum filled with fluid which clearly transilluminated Neither the testicle nor epididymis was tender on palpation In the neighborhood of the globus major, a tender, cystic, pea-sized structure could be palpated through the hydrocele fluid Prehn's sign was equivocal Laboratory studies and urinalysis were entirely negative

Preoperative impression Hydrocele, left, secondary to torsion of appendix testis

Upon opening the tunica vaginalis, 15 to 20 cc of clear yellow fluid were obtained

The globus major showed beginning erythema and edema and adjacent to it was an edematous, boggy appendix testis, which showed several blackish-blue areas upon it Inspection of its fine pedicle revealed it to be twisted, thus producing early infarction with the secondary changes noted Excision of the appendage and hydrocelectomy were performed The patient was discharged on the third postoperative day The subsequent course was uneventful

One of the pathological reports, which was typical of the others, read as follows "This vestigial organ shows a large hematoma with stagnant blood in the dilated venous spaces with resulting gangrene Diagnosis Gangrenous appendix testis"

DISCUSSION OF CASES

Not having previously encountered appendiceal torsion, at the time case 1 appeared, texts were consulted regarding diagnosis and treatment In cases 1 and 3 the usually recommended immediate surgery was not performed since spermatic cord torsion was not remotely suggested and the clinical picture seemed so benign Had case 1 been seen only in the later phase a diagnosis of epididymo-orchitis of some atypical variety would have certainly been made Case 2 is unusual in that it is the first reported case of torsion of an appendix testis simultaneously occurring with ipsilateral torsion of the spermatic cord Whether the previous episodes were due to the former or the latter is purely speculative In the cases that presented as hydroceles it is conceivable that if surgery had been delayed until even a later date, sloughing of the infarcted appendage with its subsequent absorption would have made it impossible to ever know that torsion was the original cause of the hydrocele In the acquired hydrocele a previous history of sudden pain and tenderness preceding the onset of the hydrocele by several days might be suggestive of such etiological background Whether such desquamated appendages give rise to the calcified bodies sometimes found in hydrocele cavities (corpora libera) is a matter of speculation

FINAL SUMMARY

Four cases of torsion of testicular appendages have been presented, bringing the total number reported to the present to 141. Three of the cases demonstrated the relative benignity of torsion of the appendix testis in comparison with torsion of the spermatic cord itself (case 2). If the condition is kept in mind, in adults as well as in children, in the differential diagnosis of scrotal pain, if careful attention is paid to the chronological course of events and careful palpation made the correct diagnosis will be more often made in this otherwise neglected clinical entity. If the assumption is correct that many cases are being misdiagnosed it would suggest that ultimate resolution without surgical intervention must frequently take place. However, early surgery is still advocated by most authors to reduce a subsequent period of disability by obviating secondary complications. Since the appendix testis serves no useful purpose it would seem wise to excise all pedunculated testicular appendages during any scrotal surgery.

926 S. W. Second Ave., Gainesville, Fla.

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ADRENOGENIC TESTICULAR TUMOR

ROBERT D. CROUCH

From the Department of Urology, Duke University School of Medicine and Duke Hospital, Durham, N. C.

This is the case of a testicular tumor with unusual physiological and pathological characteristics. The tumor was unquestionably adrenogenic, but the classification pathologically could not be determined. The clinical course and gross surgical findings are as follows.

A three-year-old white male child was first admitted to Duke Hospital on August 30, 1955 with the chief complaint of swelling of the left side of the scrotum of three months duration. At the onset of the swelling, he had been treated by his local physician with parenteral penicillin to no avail. He was ultimately referred to Duke Hospital with a diagnosis of probable malignancy of the left testicle. The tumor had doubled in size from the onset of the lesion until the time of admission. Previous and developmental history were entirely negative, as was the family history. The pertinent findings on physical examination were as follows: Blood pressure ranged from 135/90 to 150/100, pulse 104 to 120 per minute, respirations 20 per minute, temperature on admission 37.4 degrees centigrade. The patient was well developed, obese and in no distress. Several diffuse, small, macular lesions, some of which were pustular, were noted over the shins. There was no evidence of regional or peripheral lymphadenopathy. The heart was normal in size, and there was no evidence of abnormality on auscultation. The liver was palpable to 2 cm. below the right costal margin. Examination of the external genitalia revealed a normal uncircumcised penis. The right testicle and scrotal contents were normal. There was a large mass in the left scrotum about the size of a large orange (6 to 8 cm. in diameter) which was smooth, firm, non-tender and did not transilluminate light. The clinical diagnosis on admission was 1) testicular tumor, 2) acne, secondary to hormonal imbalance, 3) hypertension, secondary, and 4) exogenous obesity and nutritional anemia. Figure 1 shows the original appearance of the patient.

Laboratory findings revealed a hemoglobin of 9.7 gm. White blood count was 6,400 with a normal differential. Urine and stool examinations were normal. Serological test for syphilis and the O. T. test, 1:1000 were negative. Serum calcium was 9.8 and the carbon dioxide combining power was 26 meq/L. Serum chloride was 104.3 meq/L, sodium was 143.3 and potassium 4 meq/L. Fasting blood sugar was 89 mg. per cent and two hour p. c. glucose was 105 mg. per cent. Eosinophil count was 277 per cubic millimeter. The chest x-ray and plain x-ray of the abdomen were negative. Skull films and x-ray of the right hand and foot revealed normal bones for his age. Preoperative urinary steroid studies showed 17-ketosteroids of 18 mg./24 hours and 17-hydroxycorticoids of 16.7 mg./24 hours. Intravenous urograms revealed prompt and normal excretion bilaterally with a bifid pelvis and upper ureter on the left.

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Present address: 101 Office Bldg., Frederick, Md.

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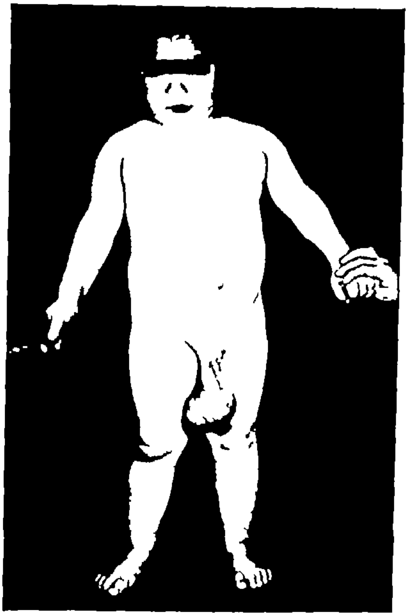

FIG 1 Adrenogenic testicular tumor

After one week in the hospital to complete the studies, the child was taken to the operating room and the left testicular mass was removed without difficulty There was no attachment to the surrounding tissue and the entire spermatic cord was removed to the internal inguinal ring He received 250 cc blood during and after surgery, but 24 hours postoperatively his blood pressure began to drop and tachycardia and signs of shock appeared He was given 200 mg intravenous hydrocortisone with good response The following day he was started on ACTH, 20 units every 12 hours and cortisone, 50 mg intramuscularly every six hours For the next five days the cortisone was tapered gradually and ACTH stopped six days postoperatively His blood pressure stabilized around 130/90 An elevation of temperature occurred two days after surgery for which achromycin and penicillin were prescribed throughout the remainder of his hospital stay Hemoglobin was 13 5 gm on discharge His acneform dermatitis became much worse, but cleared somewhat on calamine lotion At the time of discharge the pathological diagnosis was incomplete other than an undifferentiated carcinoma of the testicle which secreted adrenal hormones

Pathological report of the excised specimen was as follows "The gross specimen is identified as the left testicle It measures approximately 9 by 6 by 6 cm and has a rubbery, soft consistency The sectioned surface has a lobular, yellowish, granular appearance Some areas are soft and appear necrotic whereas other areas are somewhat more firm Representative sections of the specimen are submitted as blocks I-V It should be stated that the testicular architecture on cut surface has been completely replaced by the aforedescribed tissue "

"Microscopic The left testicle has been essentially completely replaced by a highly cellular tumor which has been separated into nodules by numerous fibrous trabeculae At the periphery of the testicle areas are present in which normal testicular seminiferous tubules are identified The tumor presents no particular picture There are areas in which the tumor is composed of sheets of relatively uniform round cells which have for the most part ill-defined cellular borders and scant cytoplasm The nuclei of these cells contain loosely arranged chromatin but sharp and well-defined borders In areas of this type mitotic figures are numerous Fibrous stroma is scant Other areas of the tumor are characterized by marked pleomorphism of the cells Some of the cells are huge and vary from a rounded shape to elongated and fusiform strap cells Some of these large cells contain hyperchromatic nuclei and acidophilic granular cytoplasm Other cells contain clear vacuolated cytoplasm Intermingled with these large cells are many pleomorphic cells of much smaller size The nuclei of these cells are hyperchromatic and well-defined Mitoses are numerous Nowhere in the tumor is there any specific pattern to the cellular structure There are multiple areas of degeneration and necrosis Scattered throughout the tumor are numerous vacuoles which stain positive for fat There is no specific cell type which makes specific classification impossible Figure 2 is a photomicrograph of a typical section through the tumor

On September 18–19 the urine 17-ketosteroid determination was 1 2 mg 24 hours and the 17-hydroxycorticoids 1 2 mg 24 hours This was the first steroid determination following surgery The patient was discharged from the hospital on September 22 1955 He was followed closely in the out-patient clinic and on October 25–26 the 17-ketosteroids were 1.2 mg 24 hours and 17-hydroxycorticoids were 1 0 mg 24 hours These were repeated for the following 24 hours and were unchanged On January 17 1956 the urinary 17-ketosteroids

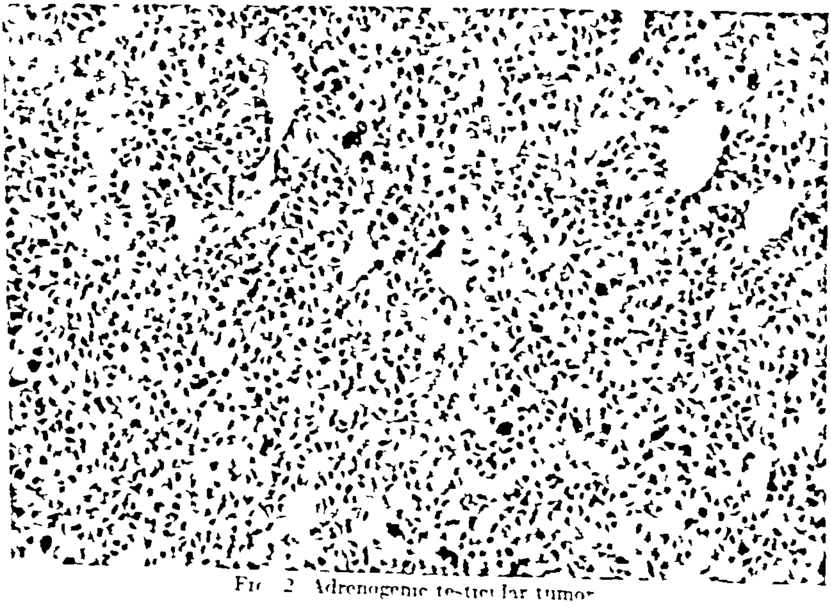

Fig 2 Adrenogenic testicular tumor

were 7 9 mg /24 hours, and the 17-hydroxycorticoids were 4 6 mg /24 hours The striking rise in the steroid excretion during the preceding two months suggested the probability of metastatic malignancy This was confirmed in May 1956, when a palpable mass was found in the left side of the abdomen The patient was again admitted to Duke Hospital on May 21, following x ray therapy at another hospital closer to his home The blood pressure on admission was 150/120 The mass in the left side of the abdomen was easily palpable The urinary 17-ketosteroids were 15 8 mg and the 17-hydroxycorticoids were 9 0 mg /24 hours A second intravenous urogram was interpreted as normal A glucose tolerance test was normal and the eosinophil count was 88 per cubic millimeter Skull x-rays were negative The patient showed evidence of a sexual and somatic precocity to a degree which had not been seen on the first admission Endocrine studies indicated a functioning, adrenal-like tumor that had not responded to x-ray therapy After these preliminary laboratory studies, he was placed on intramuscular injections of cortisone acetate to prevent the adrenal insufficiency that occurred following removal of the primary tumor

On May 28 a retroperitoneal exploration was done, and a large tumor mass adjacent to the aorta and immediately below the lower pole of the left kidney was easily removed There were numerous enlarged nodes along the aorta and the iliac vessels, several of which were removed for biopsy At the time of surgery it was believed that the nodes were metastatically involved, however, permanent pathological sections showed that they contained no evidence of metastatic tumor The large tumor mass contained no demonstrable lymphoid tissue, and was histologically identical with the original tumor of the left scrotum Postoperatively, the child was treated with cortisone acetate, which was gradually diminished in doses and replaced with ACTH gel The postoperative course was not remarkable The blood pressure stabilized at about 100/70 The child was discharged on June 4, 1956 with the final pathological diagnosis still indefinite The urinary 17-ketosteroids and 17-hydroxycorticoids were 2 8 mg and 6 7 mg per 13 hours, respectively, the day prior to discharge, indicating that there were probably other metastatic lesions present

The steroid excretions continued to rise through the last visit to Duke Hospital on September 7, 1956 Although the exact location of the metastatic lesions could not be determined at this time, it was believed that generalized carcinomatosis was present It was later learned that the patient expired at his home on September 22, 1956 An autopsy was not obtained

DISCUSSION

The foregoing case report is obviously that of an adrenogenic testicular tumor, but of an unusual type from a pathological viewpoint Dr Earl T Engle of Columbia University College of Physicians and Surgeons reviewed the case history and the microscopic slides, and the concensus of opinion of Dr Engle and his associates was that the tumor must be classified as a very embryonic and undifferentiated teratocarcinoma In view of the pathological characteristics, it is impossible to explain the increased steroid excretion However, the patient exhibited adrenal insufficiency following removal of the original testicular tumor He responded to treatment with cortisone acetate and the prophylactic administration prior to removal of the large retroperitoneal mass apparently prevented a recurrence of adrenal insufficiency It is also of interest to note the absence of metastatic lesion in the enlarged nodes that were removed adjacent to the retroperitoneal mass

SUMMARY

This has been the presentation of a rare and extraordinary testicular tumor, which could only be classified as an undifferentiated carcinoma pathologically with adrenogenic function

The author would like to thank others for their suggestions, interest, and efforts in this case namely, Dr E P Alyea, professor of urology, Duke University School of Medicine, Dr Frank L Engle and his Department of Endocrinology, and many members of the staff of the Department of Pediatrics of Duke Hospital

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THE SIGNIFICANCE OF GENETIC AND ENVIRONMENTAL FACTORS IN UROGENITAL DISEASE

CARL E BURKLAND

In urology, as in other fields of medicine, we are handicapped in the management of many diseases by dealing with the end result rather than the basic mechanisms or etiology, which are unknown Such is the situation in regard to tumor formation, urolithiasis, and congenital anomalies Since approximately 10 per cent of all human beings are born with some urogenital anomaly, and since many of these anomalies are difficult to correct, we feel that urologists should look further into the genesis of these anomalies in hope of finding a better understanding and a means of modification or prevention, if possible, which should be much better in many cases than attempted correction When a congenital malformation has a genetic basis, there is a greatly increased chance that subsequent siblings will also be malformed Murphy[1] has made a comprehensive study of congenital malformations and elicited some very significant findings He noted that in a series of 501 mothers with offspring dead of congenital defects in infancy, one-fourth (25 per cent) of subsequent pregnancies had an unfavorable outcome, half of these being live births with one or more congenital malformations The information which should be given to prospective parents having one deformed child has been thus summarized by Murphy "The offspring presenting congenital malformations which are serious enough to warrant being recorded on death certificates are approximately twenty-four times as likely to occur in families possessing a congenitally deformed child as in the population at large " Living organisms, including man, are the resultant of interaction between their heredity and environment It is our feeling, therefore, that urologists should reconsider the implications of genetic and environmental factors not only in the possible causation and prevention but also in the diagnosis, management, and prognosis of disease states of the genitourinary system

A knowledge of genetic factors can have very practical applications in other ways besides the prognosis and diagnosis of well-known hereditary diseases One example is in the detection of genetic carriers of a hereditary disease such as gout, in which 6 per cent of the patients form urinary calculi The increase of the blood uric acid level, which can usually be demonstrated among some of the relatives of a patient with gout, may indicate for those persons preventive restriction of purines in the diet together with a high fluid intake Also of practical genetic significance is that only when the donor and recipient are identical twins do homotransplantations of the kidney work successfully Of aid in the determination of sex is the work of Barr and others[2] in demonstrating that a

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Read at annual meeting of Western Section of American Urological Association, Seattle, Wash , May 27–30, 1957

[1] Murphy, D P Congenital Malformations Philadelphia J B Lippincott Co , 1947

[2] Moore, K L , Graham, M D and Barr, M L Detection of chromosomal sex in hermaphrodites from skin biopsy Surg Gynec & Obst **96** 641–648, 1953

characteristic female sex chromatin mass can be seen in the nuclei of cells of most tissues of the body, including white blood cells and cells in oral and vaginal smears Since genetic bases are known for the variability of bacteria and viruses in virulence and resistance to antibiotics, it would seem important in dealing with infectious diseases to have some understanding not only of the genetics of the human host but also genetics of the invading parasite[3]

Since the basis for the transmission of an anomaly or the susceptibility to an infectious disease is the gene, we should be aware of the newer concepts and rapid developments in regard to the biochemical nature and functions of the genes as well as the significance of various environmental factors as teratogenic agents According to Snyder[4] genes are complicated molecules of desoxyribose nucleic acid (DNA) bound up with the proteins of the chromosomes as highly polymerized nucleoproteins The basic activity of a gene now appears to be the development and production of a particular substance which has a specific effect on the metabolism of the individual In most instances this substance is an enzyme and is responsible for the catalysis of a particular step in synthesis or degradation Occasionally a normal gene is replaced by a molecule of slightly different structure, a mutant gene As a rule, the enzyme produced by a mutant gene shows a diminution or loss of activity in catalyzing the specific reaction that the normal gene accomplished In the future, we may be able to correct hereditary deficiencies by replacement of the missing enzyme with a synthetic enzyme, hormone, or chemical

Since man is a difficult animal for genetical research because his families are small, his generations slow, and his mating uncontrolled, much of our knowledge of genetic influence comes from the study of experiments on animals in which the opposite conditions prevail Bagg[5] studied the descendants of roentgen-rayed male and female mice and, beginning with the fourth generation, noticed renal anomalies which included solitary kidney, hydronephrosis, and hypoplasia By breeding males and females with the solitary kidney condition the relative frequency of incidence of this abnormality was raised considerably Hain and Robertson[6] found that as a result of the inbreeding of rats related to animals showing urogenital defects such as renal agenesia hypoplasia hydronephrosis and undescended, maldeveloped testes the incidence of the anomalies was increased They noticed that the time interval elapsing between the first appearance of the urogenital defects was the same as observed in Bagg s mice viz four generations Brown[7] studied a strain of mice derived from a previously x-rayed pair and found a high percentage of individuals with deformed or abnormal kidneys Warkany and Schraffenberger[8] noted sterility in male rats whose mothers had been exposed on the fifteenth and seventeenth day of prenatal life In an inbreeding experiment with swine, it was noted that there was a decrease in fertility, high mortality, higher percentage of stillborns, higher percentage of males, than in controls, and other characters such as cleft palate, scrotal hernia, and the ridgeling (undescended testes) character[9]

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[3] Lederberg J and Tatum E L Sex in bacteria Genetic studies Science **118** 169–175 1953

[4] Snyder L H Modern heredity and its applications Am Scientist **43** 391–419 1955

[5] Bagg H J Hereditary congenital anomalies of genitourinary organs Am J Surg **7** 211–220 1929

[6] Hain A M and Robertson J M Congenital urogenital anomalies in rats including unilateral renal agenesis further data in support of their inheritance J Anat **72** 80–100 1937

[7] Brown A L Analysis of developing metanephros in mouse embryos with abnormal kidneys Am J Anat **72** 89–100 1937

[8] Warkany J and Schraffenberger L Congenital malformations induced in rats by roentgen rays Am J Roentgenol **57** 455–463 1947

Since it is difficult in most human diseases to apply the principles of mendelian inheritance strictly, the concept of population or evolution genetics has been developed, in which it is the proportion of alleles they contain which is significant rather than the kinds of alleles When a human anomaly or disease is exclusively, or almost exclusively, determined by genetic factors, the trait is likely to be rare Human populations are so highly heterozygous that probably most people are heterozygous for some seriously harmful gene Muller has estimated that the average person is heterozygous for at least eight such genes[10]

TERMINOLOGY

For an understanding of our discussion, some definition of genetic terminology is important Space does not permit extensive definition, and for comprehensive discussion of the wide terminology and principles of genetics the reader is referred to some of the outstanding books and articles on genetics, such as those by Stern,[11] Gates,[12] Snyder,[13] Fraser,[14] and Sorsby[15]

In the somatic cells of the body the genes are paired, one member of each pair coming from the mother, and one from the father The members of a pair of genes are called 'alleles' Each member of a pair may exist in one of two states A dominant gene, by definition, is one which produces an effect in the organism, irrespective of the state of the other member of the pair (allele) A disease determined by a dominant gene will, therefore, appear in one parent of each affected individual, not appear in the offspring of two normal parents (except for the rare event of mutation), and appear in about one-half of the children of an affected person (the other parent being unaffected), each child having exactly 50 50 risk

A recessive gene is one which does not produce an effect in the presence of its dominant allele A disease caused by a recessive gene will, therefore, appear only in a person who receives two of them, one from each parent A rare, recessive inherited disease will show the following pedigree characteristics The affected person will nearly always have unaffected parents The disease may appear in the siblings of affected persons, each sibling having exactly 25 per cent risk However, because of the small size of most human families, a majority of cases will appear sporadically The parents of a patient will be 'blood relatives' more often than would be expected from the frequency of consanguineous matings in the general population Sex-linked genes are those carried in the chromosomes that determine sex

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[13] Snyder, L H Medical Genetics Durham Duke University Press, 1941

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[15] Sorsby, A Clinical Genetics London Butterworth & Co Ltd, 1953

The words 'familial,' 'hereditary,' and 'congenital have been frequently misused in the medical literature with consequent confusion The term familial' should be used only to designate the tendency of a trait or disease to run in families' to a greater degree than chance would allow Familial incidence may be due to environmental or hereditary factors Hereditary refers to inheritance of traits on mendelian principles 'Congenital means present at birth, and does not indicate etiology 'Penetrance' is a term used to indicate the ability of a gene to manifest itself, and a figure below 100 per cent indicates that other genetic or environmental factors are involved Many hereditary diseases seem to behave as dominant traits in certain families and recessive traits in others This fact, coupled with variability in penetrance, makes genetic interpretation in specific families often very difficult

How can we determine the genetic components in an abnormality? Much help can be obtained from a study of family pedigrees (which has been much neglected in regard to genitourinary anomalies), study of twins with simultaneous and symmetrical occurrence of a disease, a study of the effects of consanguinity, and a study of the results of animal experimentation

In searching for the genetic factors in any disease we must place more emphasis on the family history than merely asking the usual routine questions about cancer, heart disease, tuberculosis, etc in the family we must inquire if any other members of the patient s family had a disease similar to the patient s The rarer a disease state, the more likely it is to be hereditary An important but often a forgotten, question is in regard to consanguinity,[16] i e cousin marriage, because it is well established that if a bad defect is present in a family, consanguinity will tend to bring it out or perpetuate it, such as is often the case in cystinuria Recessive genes causing an abnormality tend to produce an abnormality more frequently in consanguineous than a nonconsanguineous marriage Another important consideration in the family history is the age of the mother Children born of mothers over 40 years of age are three times as likely to be abnormal as in mothers under 30 years

Studies in twins help to determine the genetic significance of a disorder or character The simultaneous and symmetrical occurrence of a disease such as a tumor in twins gives much credence to its hereditary origin Advanced age of the mother favors fraternal twins and multiple births and mongolism There is a much higher incidence of twins in the white and colored (black) races than in the Japanese, this being explained by the larger body size of the first two races If a child is congenitally mentally deficient, the chances of his also having structural malformation are considerably increased a point of considerable diagnostic importance in determining whether a presenting syndrome is congenital or acquired

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[16] Fraser F C Consanguinity and its significance in the family history Canad Med A J 66 258–260 1952

While it is very difficult, and impossible in many cases, to say that a condition is entirely hereditary or entirely environmental, the important consideration is the percentage of the relative roles each of these plays in regard to one another in the production of the finished character Genes cannot operate in a vacuum, but must obtain their expression through effects on the cytoplasm of the organism The genetic pattern of an organism may be modified by such environmental factors as temperature, infection, moisture, oxygen deficiency, malnutrition, hormones, and drugs Malformations have been produced experimentally in animal young when the fetal environment has been influenced by chemical, endocrine, mechanical and actinic factors To be effective, the latter must exert their influence in the organogenetic period of embryonic development, that is, in the first few days or weeks of embryonic development when differentiation of the various organs and systems is taking place Cryptorchism has been noted when pregnant mice were subject to hypoxia[17] and vitamin A deficiency [18] Hypospadias has been noted in rats whose mothers had been on a vitamin A deficiency diet[18] and in humans whose mothers had suffered from rubella during early pregnancy [19] Maternal vitamin A deficiency[20] has been found to induce fused kidneys, solitary kidneys, and ectopic kidneys in both rats and pigs Nelson and associates[21] noticed among multiple congenital anomalies marked retardation of development of the kidneys in young rats born of mothers suffering from pteroylglutamic acid deficiency Warkany[22] found female rats with insufficient riboflavin have young with skeletal abnormalities, thin abdominal walls in ventral midline, protrusion of the viscera, and defective eyes Horseshoe kidneys and bilateral or unilateral renal agenesia were noted as a reaction of fat embryos to irradiation after tenth-day exposure, by Wilson [23] Sex reversal in the lower, and pseudohermaphroditism in higher, animals have been produced by sex hormones Included in Moore's extensive review on the role of fetal endocrine glands in development is an analysis of the genital and other changes produced by hormones [24] It appears that there are a host of teratogenic agents, but that it is not so much the nature of the agent as the timing of its administration during the period of fetal gestation that is the important factor in the production of anomalies Malnutrition (human), as indicated in several studies made during and shortly after wars, depressions, and in people of low income, has not been productive of a higher incidence of defective children than in well-nourished parents However, if the greatest effect of malnutrition is exercised during the first few weeks of embryonic life, it does not seem unreasonable to expect the production of some anomaly

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[17] Ingalls, T H , Curley, F J and Prindle, R A Experimental production of congenital anomalies New Eng J Med , **247** 759–765, 1952

[18] Wilson, J G and Warkany, J Malformations in the genitourinary tract induced by maternal vitamin A deficiency in the rat Am J Anat , **83** 357–407, 1948

[19] Swan, C , Tostevin, A L , Moore, B , Mayo, H and Black, G H B Congenital defects in infants following infectious diseases during pregnancy Med J Austral , **2** 201–210, 1943

[20] Warkany, J Disturbance of embryonic development by maternal vitamin deficiencies J Cell & Comp Physiol , **43** 207–236, 1954

[21] Nelson, M M , Asling, C W and Evans, H M Production of multiple congenital abnormalities in the young by maternal pteroylglutamic acid deficiency during gestation J Nutrition, **48** 61–80, 1952

[22] Warkany, J Etiology of congenital malformations Advances in Pediat , **2** 1–63, 1947

[23] Wilson, J G Differentiation and the reaction of rat embryos to radiation J Cell & Comp Physiol , **43** 11–37, 1954

[24] Moore, C H The role of the fetal endocrine glands in development J Clin Endocrinol , **10** 942–985, 1950

How can we make practical applications of animal results to human cases? We can do so by judicious inference while accumulating more data There is great concern over the pathological effects of increased exposure to irradiation by man from cosmic irradiation, atomic bomb explosions, occupational uses, and from the widespread use of x-rays for diagnostic and therapeutic work The latter is the greatest contributor to the exposure of present populations The genetic effects come from the mutations induced by irradiation, which are considered to be a fruitful source of future anomalies Irradiation of the pregnant uterus will also cause direct harm to the developing embryo Since it is generally considered that most mutations are deleterious, and since it is the total cumulative dose to which the number of induced mutations is proportional, urologists as well as all other physicians should be very judicous in their use of x-rays in diagnostic and therapeutic work The time may soon be here that for medicolegal as well as scientific reasons we may be forced to shield the pelvis and gonads, particularly in women in the child-bearing period, in taking pyelograms, which will largely be limited to demonstration of the kidneys

CLINICAL CONDITIONS WITH KNOWN GENETIC FACTORS

There are several urological conditions in which hereditary factors have been noted In table 1 are listed congenital abnormalities of the urogenital system in which hereditary features have been noted, and their probable mode of inheritance

James[75] has reported four cases of aplasia of the male prepuce with evidence of hereditary transmission in which the child was considered to have been 'born circumcised ' Hypospadias has been observed to occur in several families, in twins, in father-and-son combinations, by several men, including the writer It is a form of intersexuality and often associated with cryptorchism Genetically, it is considered as an irregularly recessive defect, but it may be dominant, transmitted through normal females as well as normal or affected males It is seen most frequently in boys born of young mothers and often in the first-born Sorenson[76] noted a family history of hypospadias in 29 of 103 cases which he investigated in Denmark In a survey of the literature, Kemp[77] found records of 56 families in which it occurred in brothers, of 9 in which it affected father and son, of 3 involving grandfather, father, and son Hypospadias appeared in

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[75] James T Aplasia of the male prepuce with evidence of hereditary transmission J Anat 85 370-372 1951

[76] Sorenson R The Etiology of Hypospadia Copenhagen Munksgaard Op Dom Biol hered hum KBh 31

[77] Kemp T Genetics and Disease Copenhagen 1951, Ejnar Munksgaard

TABLE 1

Anomaly	Mode of Inheritance	Anomaly	Mode of Inheritance
Aplasia of prepuce	D	Megaureter	R
Hypospadias	D or R	Polycystic kidney (adult)	D
Epispadias	R?	Polycystic kidney (infant)	R
Cryptorchism	R?	Duplication of kidney and ureter	D
Atresia vaginae	R?	Adrenogenital syndrome	S R
Valves of posterior urethra	R	Intersexuality (hermaphroditism)	S R
Median bar	R?	Gynecomastia	R
Renal agenesis (bilateral)	R	Eunuchoidism	R
Renal agenesis (unilateral)	R	Laurence-Moon Biedl syndrome	R
Horseshoe kidney	R	Pubertas praecox	R?
		Klinefelter's syndrome	R

D—dominant R—recessive S R—sex linked recessive

5 successive generations in 2 families and in 6 successive generations in one family Culp[28] has reviewed 172 cases of hypospadias upon which he has operated and noted 5 families in which 2 sons had sufficient chordee and hypospadias to require surgical treatment, but no twins He has seen one adult cured of hypospadias by Havens at age 16, who begat a son with hypospadias that requires operation Culp also noted that about 15 per cent of his hypospadias cases had cryptorchism and that approximately the same percentage of cryptorchids had hypospadias Smith,[29] in a large personal series, has noted hypospadias in several siblings The writer has seen a father and son with penile hypospadias Lingaard[12] has described a family with male-to-male inheritance through 6 generations The patient is fortunate that hypospadias is a correctible hereditary defect

Cryptorchism is commonly seen, but few observations on its familial incidence have been noted In dogs and pigs it is observed as a simple recessive O'Conor and Corbus[30] have described the familial occurrence in 6 brothers Goebel[31] has treated a father and son for cryptorchism, both on the right side Murphy[32] has treated an uncle and nephew with cryptorchism on the left side Thus, we may consider cryptorchism as an example, like hypospadias, of a genetic defect correctible by surgery

Congenital valves in the posterior urethra have been described in a pair of one-egg twins with undescended testes, by Newberger and Davidsohn [33] Congenital median bars occurring in 27-year old twins and giving urinary symptoms and identical cystoscopic malformations at the same time, have been reported by

[28] Culp, O S Personal communication

[29] Smith, D R Personal communication

[30] Corbus, B and O'Conor, V Pedigree of cryptorchidism Surg , Gynec & Obst , 34 237–240, 1922

[31] Goebel, J H Personal communication

[32] Murphy, W Personal communication

[33] Newberger, C and Davidsohn, I Congenital valves of posterior urethra in twins Arch Path , 16 55–62, 1933

Wilhelmi[34] Finkle and associates[35] have recently reported on two young brothers, aged six and five years, who were found to be uremic from congenital contracture of the bladder neck Atresia of the vagina has been noted in 2, and imperforate hymen in three sisters[36] These, too, are all defects amenable to surgery

Schmidt and associates[37] have reported two cases of bilateral renal agenesis occurring in nontwin sisters, and Madisson,[38] two cases in nontwin brothers Congenital renal agenesis has been observed in a maternal uncle and nephew, by Bound[39] Mackay[40] has reported 3 cases of megaloureter (2 bilateral), with hydronephrosis, occurring in a family of seven siblings The paternal grandfather died of pyonephrosis, so he may have had a congenital hydronephrosis Polycystic renal disease[41] is the best-known form of urologic anomaly that shows a strong familial hereditary tendency, but what is not so widely known is that there are two distinct hereditary types—a recessive type leading to death in infancy, and a dominant type which ordinarily does not cause symptoms until early adult life It seems to the writer that there is a decided absence of pyelographic records of early or developing polycystic disease, and if we secured pyelograms on all the siblings and close members of the afflicted patient's family, we could probably get a better understanding of the abnormality

Familial duplication of kidney and ureter has been infrequently described in the literature Girsh and Karpinski[42] have reviewed the literature and found five families in which this occurred, and reported a sixth family of their own in which three members (all female) of a family of four had upper urinary tract duplication We wish to report here on 3 instances of reduplication of kidney and ureter seen by us in a family of five, all of whom at one time or the other were also under observation for urinary tract infections Details are presented in table 2

Attempts to secure further detailed information, including pyelograms, on other living relatives of mother and father have so far been unsuccessful, but there is no known kidney trouble in other relatives There is no history of consanguinity Since reduplication of the upper urinary tract is a very common anomaly, and since it is prone to cause complications, it appears very advisable to secure pyelograms of the relatives of any patient who has this anomaly

There is a group of anomalies with a particular association of genetic and

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[34] Wilhelmi O J Congenital median bars occurring in twins J A M A, 101 847–849, 1933

[35] Finkle A L McPhee V C and van der Reis L Congenital bladder neck contracture in male siblings Calif Med 85 260–264 1956

[36] McIlroy A L and Ward I V Three cases of imperforate hymen occurring in one family Proc Roy Soc Med 23 13–14 1930

[37] Schmidt E C H Hartley A A and Bower, R Renal aplasia in sisters Arch Path 54 403–406 1952

[38] Madisson H Über das Fehlen Beider Nieren Zentralbl Allg Path 60 1–8, 1934

[39] Bound J P Two cases of congenital absence of one kidney in same family Brit M J 2 747 1943

[40] Mackay H Congenital bilateral megaloureters with hydronephrosis a remarkable family history Proc Roy Soc Med 38 567–568 1944–45

[41] Fergusson J D Observations of familial polycystic disease of the kidney Brit J Urol 21 241–242 1949 also Proc Roy Soc Med 42 806–814 1949

[42] Girsh I S and Karpinski F I Urinary tract malformations Their familial occurrence with special reference to double ureter double pelvis and double kidney New Eng J Med 254 855 1956

TABLE 2 *Occurrence of double kidney and double ureter in family S*

Member of Family	Age	Description of Duplication	Pathology	Surgery
Father (B S)	48	0	Nephrolithiasis and pyelonephritis, left	Nephrolithotomy
Mother (C S)	40	*Unilateral, left, complete* double ureter, pelvis, and kidney	Dilated ureter containing 9 stones, going to hydronephrotic upper pelvis	Heminephrectomy, left
Daughter (S L)	27	Complete, bilateral, double ureter, pelvis, and kidney	Hydronephrotic atrophy of upper half, severe pyelonephritis of lower half of left kidney	Nephrectomy, complete, left
Daughter (C W)	19	Unilateral, left, complete duplication of *ureter, pelvis and* kidney	Urinary tract infection	0
Granddaughter (S L) (daughter of S L)	4	0 (Normal pyelogram)	Urinary tract infection	0

endocrine factors [43] [44] One such is the adrenogenital syndrome which with or without adrenal hyperplasia has been observed in one-egg twins, in a mother and daughter, and in several siblings, and is considered to be a sex-linked recessive character Bentinck and associates[45] reviewed the literature in the familial congenital adrenal syndrome and reported on 2 cases of their own They noted 43 families in which 100 instances of somatosexual abnormality were recorded, largely female pseudohermaphrodites Intersexuality, as expressed in the various forms of hermaphroditism, has a strong genetic background which in many instances appears to have been modified by the sex, adrenal, and other hormones [46] [47] The effect of excessive androgens during gestation on the female fetus is to produce hermaphroditism This is most commonly seen in the intersexual changes found in persons with congenital adrenal hyperplasia Similar changes have been reported in two cases in which there were arrhenoblastomas in the mothers during pregnancy[48] and in infants whose mothers received testosterone during pregnancy [49] The administration of testosterone to rhesus monkeys during generation also results in pseudohermaphrodites Male pseudohermaphroditism has been observed in 17 families in 2 brothers in 2 families in 3 brothers and in one family in 4 brothers Hirschfeld [5] observed consanguinity among the parents of pseudohermaphrodites in 37 per cent In many of the cases the anomaly is inherited through normal females Both male and female pseudohermaphroditism are genetic defects which have been proven amenable to amelioration by surgery and the female form also by cortisone

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[43] Biggs, R and Rose, E The familial incidence of *adrenal hypertrophy and female* pseudohermaphroditism J Obst & Gynec , Brit Emp , **54** 369, 1947

[44] Collier, T W *Pseudohermaphroditism in twins, report of the tenth case* Am J Dis Child , **76** 208–212, 1948

[45] Bentinck, R C , Hinman, F , Lisser, H and Traut, H F The familial congenital adrenal syndrome Report of two cases Post Grad Med , **2** 301–312, 1952

[46] Wilkins, L *The diagnosis of the adrenogenital syndrome* and its treatment with cortisone J Pediat , **41** 860–865, 1952

[47] Greene, R R , Burrill, M W *and* Ivy, A C Experimental intersexuality Production of feminized male rats by antenatal treatment with estrogens Science **88** 130–131 1938

[48] Javert, C T and Finn, W F Arrhenoblastoma Incidence of malignancy and relationship to pregnancy, *to sterility and to treatment* Cancer, **4** 60–77, 1951

[49] Hayles, A B and Nolan, R B Female pseudohermaphroditism Report of a case in an infant born *of a mother receiving* methyltestosterone during pregnancy Proc Staff Meet

Eunuchoidism or hypogenitalism is often familial Young has reported three cases of gynecomastia associated with hypogenitalism and lack of development of the prostate accompanied by sterility 2 of them being in brothers Reifenstein has described a syndrome of familial hypogonadism with various manifestations such as hypospadias sterility gynecomastia small testes and late puberty affecting nine of 10 male members of one family in two generations Roth has reported on four cases of eunuchoidism in brothers having other features besides hypogenitalism (obesity mental deficiency retinitis pigmentosa and polydactyly) to produce a symptom complex known as the Laurence-Moon-Biedl syndrome The latter is considered to be the effect of a pleiotropic gene i e one which causes several abnormalities in one individual The gene is considered to be autosomal recessive and for it a carrier state exists A high frequency of parental consanguinity has been noted in the syndrome Pubertas praecox as well as macrogenitosomia has been noted several times in siblings and their parents Jacobsen and Macklin have described a family in which 27 members were affected with hereditary sexual precocity Engstrom and Munson have presented clinical and laboratory data on a family in which father and two sons showed precocious genital and somatic growth Klinefelter's syndrome (characterized by gynecomastia aspermatogenesis without aleydigism and increased excretion of follicle-stimulating hormone) has been noted to occur in families

There are several varied urogenital lesions in which genetic or familial factors have been noted Some of these are listed in table 3

Champlin has recorded an instance of tumor of the testes (embryonal carcinoma) in identical twins The tumor occurred in both on the right side in the first twin at 20 years of age and the second at [illegible] The first twin had an injury to his testes and this may have been why his tumor antedated his brother's by

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van Wagenen G and Hamilton J B Experimental production of pseudohermaphroditism in monkeys Essays in Biology Los Angeles University of California Press 1943 p 583

Young H H Genital abnormalities hermaphroditism and related adrenal diseases Baltimore Williams & Wilkins Co 1937

Reifenstein E C Hereditary familial hypogonadism Proc Am Fed Clin Research 3 [illegible] 1947

Roth A A Familial eunuchoidism The Laurence-Moon-Biedl syndrome J Urol 57 [illegible] 1947

Jacobsen A W and Macklin M T Hereditary sexual precocity report of a family with 27 affected members Pediat 9 [illegible] 1952

Engstrom W W and Munson P L Precocious sexual and somatic maturation in [illegible] hormonal and chemical [illegible] Am J Dis Child 81 [illegible] 1951

Champlin H W [illegible] embryonal carcinoma in identical twins J A M A 95 [illegible] 1930

TABLE 3

Anomaly	Mode of Inheritance	Anomaly	Mode of Inheritance
Tumor of testis	R?	Pheochromocytoma	D?
Carcinoma of prostate	R?	Pyelonephritis	S-D?
Benign prostatic hypertrophy	D?	Sterility	D?
Wilms' tumor	R?	Enuresis	D
Adrenal hyperplasia	R	Orthostatic albuminuria	D?

D—dominant R—recessive S-D—sex dominant

five years Wells[57] is also said to have noted tumors of the testes in twins Fister[58] has reported on two cases of carcinoma of the prostate occurring simultaneously in identical twins Wilms' tumor has been noted in siblings,[40] as has adrenal hyperplasia Calkins and Howard[59] have recorded a family in which a young woman and her maternal aunt both showed multiple pheochromocytomas Her mother had probably died from the same affection

Sturtz and Burke[60] have reviewed the literature and reported a family of 12 members afflicted with a condition marked by hereditary hematuria, nephropathy and deafness, which appears to be a definite genetic entity The disease is characterized in males by the presence of hematuria, albuminuria, cylindruria, nerve deafness usually, and progressive renal disease, death occurs at an early age The disease is characterized in females by the presence of hematuria, albuminuria, cylindruria, and occasional nerve deafness, the course of the disease is relatively benign except during pregnancy, when hypertension, edema, and other signs of toxemia may occur

In a study in which 134 living members of a kindred of 232 descendants of a single person in 4 generations were examined, Perkoff and associates[61] have described a family "in which 50 members have renal disease with the characteristics of chronic interstitial pyelonephritis but in which progressive renal insufficiency develops only in the males " Eight males had died of the disease Autopsy in three of the eight cases showed that the patients had had chronic interstitial pyelonephritis Six of the eight had had nerve deafness The urine of 44 members of the family was examined, proteinuria and pyuria were the major abnormalities, although the urine of five members contained pathogenic bacteria Fourteen persons of this family were deaf These authors concluded that "the nephritis in this kindred is related to the transmission of an incompletely sex-linked dominant gene " This disease is set apart from hereditary hematuria, nephropathy, and deafness, by pyuria and the pathologic finding of pyelonephritis

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[57] Wells, H G Quoted in Twinem, F P Identical twins and problems of heredity N Y State J Med , **27** 1192–1193, 1927

[58] Fister, G A Carcinoma of the prostate in twins J Urol , **57** 488–494, 1947

[59] Calkins, E and Howard, J E Bilateral familial phaeochromocytomata with paroxysmal hypertension, successful surgical removal of tumors in 2 cases, with discussion of certain diagnostic procedures and physiological considerations J Clin Endocrinol , **7** 475–492, 1947

[60] Sturtz, G S and Burke, E C Hereditary hematuria, nephropathy and deafness New Eng J Med , **254** 1123–1126, 1956

[61] Perkoff, G T , Stephens, F E , Dolowitz, D A and Tyler, F H A clinical study of hereditary interstitial pyelonephritis Arch Int Med , **88** 191–200, 1951

The study in this large kindred appears to indicate that renal infection may occur in families on a basis of direct genetic susceptibility and gives further reason why the control of pyelonephritis with all known measures, including antibiotics, proves so difficult in many cases The matter of genetics in relation to bacteria and viruses and the problem of urinary tract infection is very important and complex, space does not permit adequate discussion here Further research in this field should prove very fruitful and practical to urologists

The problem of sterility is difficult and of much concern to patient and doctor alike Recessive mutations causing sterility have been noted in animals Inbreeding of hogs and mice has decreased fertility A pedigree showing many sterile or partly sterile males is given by Crew and Miller [62] Kup has recorded a pedigree with sterility in both sexes [63] Stern[64] has reported on genetic observations in a strain of mice where pituitary insufficiency due to a recessive gene is a cause of sterility Stern has described a family pedigree going back 250 years in which the individual male members of the family were of low fertility and their functioning sperm, producing sons almost exclusively, were only of the Y-chromosome-carrying kind I have observed twin brothers who are normal in all respects, including their semen analysis, married several years, one twin to a second wife, who have not been able to produce pregnancy in their wives, who are considered normal Stern admits the problem is very difficult and states that there can not be a single type of inheritance of sterility but rather a great many types must exist It may be that there is a deficiency of DNA in the sperm cells of the infertile male compared to the fertile male

Orthostatic albuminuria has been noted to run in families

I have observed a familial history of enuresis in several patients and have also often noted that the child tends to stop bed-wetting about the same age the mother or grandmother did I feel that given a family history of enuresis, studies as to its possible etiology need not be too exhaustive

It is in connection with certain metabolic disorders, largely of urological significance because of stone formation as a complication, that newer developments in the field of biochemical genetics seem to offer the greatest hope for not too distant practical application

Alkaptonuria[65] is a classical example in chemical genetics, being the first instance in which a particular gene was related to a specific and known biochemical reaction A characteristic symptom is the blackening of urine on exposure to air, due to the presence of homogentisic acid, or alkapton It is recognized that alkaptonuria behaves as a simple mendelian recessive There is a high frequency of consanguineous marriage among the parents The blood serum of normal individuals contains an enzyme capable of catalyzing the breakdown of homogentisic acid, but this enzyme is apparently absent from the sera of alkaptonurics. As a complication, severe osteoarthritis may develop, and also in a few cases stones may be formed in the urogenital tract.[66]

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[62] Crew F A E and Miller W C Human sterility of unusual pedigree Eugen Rev, 23 127-128 1931

[63] Kup J A Cited by Sorsby

[64] Stern C Genetic aspects of sterility Fertil & Steril 1 407-414 1950

[65] Garrod A E Inborn Errors of Metabolism London Oxford University Press 1923

Gout, a disorder of uric-acid metabolism of considerable urological significance because of the high incidence of formation of nonopaque urinary calculi, is considered to be of dominant inheritance, with penetrance and expressivity that are often irregular. What is inherited is the tendency to hyperuricemia. Since the increased chemical levels in the blood precede clinical manifestations of the disease, we have a method of detecting genetic carriers. By advising the proper low-purine diet and high fluid intake, we can forestall full development of the condition and calculous formation.

Gout is an example of sex-controlled heredity with a predilection for men, 90–95 per cent. Smyth, Cotterman, and Freyberg[67] have made biochemical and genetic investigations of gout in families. They showed that the concentration of uric acid in the blood was higher in the male than the female members of affected families, and that in each case of gout at least one parent was hyperuricemic, as were also about 50 per cent of the sibship. Only 10 per cent of those with hyperuricemia showed clinical gout. There were as many cases of transmission of the condition by women as by men. Gout is an example of a genetic defect which under the influence of environment (improper diet) expresses itself in later life.

Whatever the detailed mechanisms turn out to be, it seems that a picture is emerging of a detailed genetical control at many different points in the process of tubular resorption function. Cystinuria is a hereditary condition in which a defect in tubular function appears as a cause of the disorder. Dent[68] has found that patients who form cystine calculi in the kidneys excrete in their urine not only cystine but also the basic amino acids (lysine, arginine, and ornithine) in grossly increased amounts. Cystinurics who do not excrete arginine also do not form stones. In some families the gene responsible for cystinuria acts as a dominant and in others as a recessive. Parental consanguinity is noted in some cases. Dent[69] has presented the hypothesis that the abnormality in cystinuria is of renal origin. He thought the renal tubules might be unable to reabsorb cystine, lysine, arginine, and ornithine normally present in the glomerular filtrate, and these substances would therefore appear in large amounts in the urine. Further studies on the normal plasma levels of cystine and the other amino acids, their high excretion in the urine, clearance studies in cystinurics, and feeding experiments, have yielded evidence in favor of the renal hypothesis, which implies that in cystinurics the renal tubular reabsorption of amino acids is defective. When the urine from healthy relatives of patients with cystine stone formation is examined, it is found that a number of them, though quite well, nevertheless excrete cystine and lysine in unusual amounts in their urine. Thus, a particular abnormal gene may lead to a highly specific disturbance in renal tubular reabsorption process and the degree of this disturbance may be related quantitatively to whether an individual possesses the genes in single or double dose[70]

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[66] Young, H. H.: Calculi of prostate associated with ochronosis and alkaptonuria. J. Urol., **51**: 48–58, 1944.

[67] Smyth, C. J., Cotterman, C. W. and Freyberg, R. H.: Genetics of gout and hyperuricemia. J. Clin. Investig., **27**: 749–759, 1948.

[68] Dent, C. E., Heathcote, J. S. and Joron, G. E.: The pathogenesis of cystinuria. J. Clin. Investig., **33**: 1210–1215, 1954.

[69] Dent, C. E. and Harris, H.: The genetics of cystinuria. Ann. Eugen., **16**: 60–87, 1951.

Abnormal genes are known which lead to a diminished capacity for tubular reabsorption of glucose and phosphate[70] Idiopathic hypercalciuria[71] responsible for a high proportion of kidney stones apparently represents a genetic inability of the tubule to resorb calcium in proper amounts It is important however to distinguish this primary type of calcium deficit from those that occur as secondary responses to such stimuli as hyperparathyroidism immobilization of the skeleton, chronic acidosis high calcium intake or vitamin D poisoning

While the hereditary influence in urolithiasis is clearly revealed only in cystinuria renal calculi of the ordinary types have been recorded in twin sisters and siblings Gram[72] has studied the dominant transmission of oxaluria in an extensive pedigree which included 4 generations comprising 15 individuals Except for 2 doubtful cases the affection manifested itself only in males, whereas the transmission took place through both sexes There was also concordant manifestation in a set of twins Goldstein[73] has commented on the familial incidence in urolithiasis I have one patient whose brother, father and two paternal uncles have had kidney stones and another patient whose brother and mother have renal stones, all living in different parts of the country

Fanconi s syndrome[74-76] is a disorder characterized by a disturbance of renal tubular function resulting in decreased reabsorption of glucose phosphates, amino acids and fixed base It has been labeled as hypophosphatemic rickets with acidosis It is a hereditary disease the milder forms being transmitted as a dominant characteristic, the graver forms, as a mendelian recessive Cystinosis characterized by abnormal deposition of cystine crystals in the body tissues, including the renal tubules may manifest itself as Fanconi s syndrome

Other clinical syndromes produced by isolated dysfunctions of the renal tubule which may involve hereditary factors and possible urological implications include nephrogenic diabetes insipidus[77] vitamin D-resistant rickets[78] and hyperchloremic acidosis with nephrocalcinosis[79] There are two types of familial

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Harris H Genetic Aspects of Tubular Function in Modern Views on Secretion of Urine The Cushny Memorial Lectures Boston Little Brown & Co 1956

[71] Flocks R H Prophylaxis and medical management of calcium urolithiasis, role of quantity and precipitability of urinary calcium J Urol 44 183-190 1940

Gram H C Heredity of oxalic urinary calculi Acta Med Scand 78 268-281 1932

[73] Goldstein A E Familial urological disease Am Surg 17 84-92 1951

[74] Albright H and Reifenstein E C Jr Parathyroid Glands and Metabolic Bone Disease Selected Studies Baltimore Williams & Wilkins Co 1948

[75] McCune D J Mason H H and Clarke H T Intractable hypophosphatemic rickets with renal glycosuria and acidosis (the Fanconi syndrome) Am J Dis Child 65 81-146 1943

[76] Jackson W P U and Linder G C Innate functional defects of renal tubules with particular reference to the Fanconi syndrome Case with retinitis pigmentosa Quart J Med 22 133-156 1953

Forssman H On hereditary diabetes insipidus with special regard to sex linked form Acta Med Scandinav supp 159 pp 1-196 1945

[78] Fanconi G Disturbances in calcium and phosphorus metabolism Metabolism 4 95-106 1955

[79] Schreiner G E Smith L H Jr and Kyle L H Renal hyperchloremic acidosis Familial occurrence of nephrocalcinosis with hyperchloremia and low serum bicarbonate Am J Med 15 122-129 1953

diabetes insipidus The first, of the pituitary type, is responsive to the antidiuretic effect of pitressin and may represent a dominant or sex-linked pattern of inheritance [80] The second, of the nephrogenic type, is due to a sex-linked recessive defect which impairs the ability of the distal tubular segments to reabsorb water, is not responsive to pitressin, occurs only in males, and is transmitted by females [81] Chronic phosphate diuresis results in a type of rickets that is relatively resistant to vitamin D, it is a dominant trait and may represent a deficiency of phosphatases and phosphorylases in the proximal tubule The syndrome of renal tubular acidosis has been described under a complexity of titles Urological interest in this disease stems from the complex physiologic alterations accompanying it and the fact that nephrolithiasis and nephrocalcinosis may be seen as complications

In connection with the first type of diabetes insipidus, Weller and associates[82] have carefully studied five patients in a family and observed identical changes in the urinary tract of each member, of special interest to urologists There was great hypertrophy of the vesical detrusor muscle and internal sphincter, increased bladder capacity, enormous dilatation of the ureters and renal pelves, and elevation of the blood nonprotein nitrogen and blood pressure They felt that the enormously increased urinary output initiated a corresponding increase in physiologic activity of the bladder, leading to these changes

In table 4 are listed some miscellaneous medical conditions with genetic factors which have been selected as significant because of their possible urological complications or implications, and their probable modes of inheritance

The vascular lesions are always important because of difficulties they cause with hemorrhage and shock during surgery, complications of embolism or thrombosis to or in the kidney, and likelihood of severe acute and chronic renal insufficiency which may develop during their course Their familial background is under more intensive study [83] Severe hemorrhage in, or as a complication of, surgery on the urogenital tract is always a hazard in hemophilia Hematuria, unexplained, or difficult to treat, as well as priapism, may be a complication of sickle cell disease, which is considered to be due to the inheritance of defective hemoglobin molecules [84]

Urologists must differentiate sickle cell anemia, in which the red blood cells contain abnormal hemoglobin S, sickle cell trait, in which the red blood cells contain normal hemoglobin and abnormal hemoglobin S, and sickle cell hemoglobin C disease, in which red blood cells contain both abnormal hemoglobins S and C Gross hematuria is most apt to occur in sickle cell trait and sickle cell hemoglobin C disease [85] All these abnormal hemoglobin diseases occur in Negroes

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TABLE 4

Disease	Mode of Inheritance	Disease	Mode of Inheritance
Nephrosclerosis	D	Diabetes	D
Essential hypertension	D	Allergy	D
Glomerulonephritis	D	Angioneurotic edema	D
Hemophilia	S R	Spina bifida occulta	D
Sickle cell disease	D or R	Paget's disease	D
Leukemia	R	Porphyria	R
Congenital afibrinogenemia	R	Neurofibromatosis	R

When hematuria occurs, nephrectomy (which has been performed mistakenly several times) is contraindicated Leukemia may cause urinary tract hemorrhage or infiltration into the kidney or prostate, leading to diagnostic and therapeutic difficulties[56] Afibrinogenemia, due to an incomplete recessive gene, is a rare disease characterized by the absence of blood fibrinogen, with incoagulability of the blood and a consequent tendency to fatal hemorrhage Diabetes has urological significance because of the hazard of surgery, and complications such as necrotizing papillitis and neurological bladder Many allergic manifestations[57] are considered to be hereditary, and there is the possibility of sensitization in the genitourinary system Angioneurotic edema[58, 59] involving the prepuce and scrotum has been noted to occur in father and son Involvement of the genitals has caused urethral occlusion Cases are also on record simulating renal colic, from involvement of abdominal organs Spina bifida occulta may be a cause of neurological bladder Paget's disease has significance in the differential diagnosis of metastases from carcinoma of the prostate by x-ray and the possibility of urinary calculi formation if the patient is not active

Porphyria is of urological significance in the differential diagnosis of severe abdominal pain which may occur with it and simulate renal colic Adrenal tumors may be found in association with neurofibromatosis, which may be hereditary There are undoubtedly many other hereditary medical diseases with possible urological implications, but the above-mentioned miscellaneous group is fairly representative of the more common conditions seen with urological manifestations or complications

SUMMARY AND CONCLUSIONS

Since any finished character is the cooperative result of hereditary and environmental influences, the significance of these factors has been analyzed in several urogenital conditions and medical diseases with urological implications The newer developments in regard to the biochemical nature and functions of the gene as an enzyme expressing itself in a modifiable environment, the inferences from results of animal experimentation on hereditary and teratogenic factors, and clinical observations of genetic factors, have been discussed Some specific practical applications of our knowledge of human heredity have been developed These include first, genetic prognosis, that is, giving advice on prospective marriages and prospective families, second, diagnosis, on the basis of the family history, of conditions difficult to identify accurately by other means, third, instituting preventive measures against certain diseases on the basis of known genetic background, fourth, testing, paternity, and other medicolegal problems, on the basis of various blood groups, and fifth, evaluation of eugenic programs for the protection and improvement of society

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The accumulating evidence is that the primary action of all noxious agents is to inhibit the rate of development of the embryo, and that the type of resulting deformity depends upon the developmental moment at which the interruption occurs X-rays and thermonuclear weapons have been singled out by the Medical Research Council committee on radiation hazards as the two sources of radiation most responsible for cumulative and irreparable somatic and genetic changes to individuals, their offspring, and the human race In view of these considerations, urologists, who are large users of irradiation in various forms, should be very judicious in their employment of this agent for diagnostic and therapeutic purposes

The metabolic and other diseases related to genetic tubular dysfunction through altered enzyme activity, which are of interest to urologists because of the frequency of stone formation in the urinary tract as a complication, are becoming better understood The newer avenues of study through chromatography and electrophoresis are identifying new substances and new functions It is predicted that practical clinical applications in the management of this group of hitherto poorly understood conditions will soon be forthcoming

The attitude of hopelessness regarding hereditary defects should be abolished since several of these are now correctible or modifiable by surgery or drugs, in light of increasing scientific knowledge, we can expect many more to be so in the foreseeable future Furthermore, since there is a tremendous increase in the number of persons reaching the higher age brackets, more consideration should be given to the interaction of genetic traits and the aging process

The seventh family in which reduplication of the upper urinary tract has been noted, is recorded This anomaly is of sufficiently frequent occurrence and importance, because of complications, to warrant the taking of pyelograms on all relatives of any afflicted patient

Our knowledge of genetics in human disease, especially in the field of urology, is very inadequate In order to draw more definite conclusions and find practical applications of genetics, we should all accumulate more data on the hereditary backgrounds of various urogenital conditions This involves paying more attention to taking the patient's family history It would prove very beneficial if this information were deposited in one or more of the institutions devoted to the study of human genetics, located in different parts of the country We could then have a registry of family pedigrees of urological diseases which could prove just as valuable as our tumor registry

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BACTEREMIC SHOCK SEQUEL TO GENITOURINARY TRACT INSTRUMENTATION

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Bacteremic shock is a disease entity which has received considerable attention in the recent medical literature, but, to our knowledge, has not been discussed from the urologic viewpoint This would appear to have value, because, in the cases presented in the literature, the genitourinary tract was the portal of entry of the bacteria in 50 to 75 per cent of the cases In addition, the majority of these cases had obvious inciting operative or diagnostic instrumentation The mortality rates ranged from 25 to 75 per cent, depending on the adequacy or inadequacy of the treatment administered

Hall and Gold[1] recently reported that of 35 patients who had shock associated with a bacteremia, the genitourinary tract was the most frequent portal of entry Of 15 patients, 13 had had recent urethral instrumentation or surgery, and two had abscesses These procedures included cystoscopy, cystogram, retrograde pyelography, urethral catheterization and prostatectomy The mortality rate was 51 per cent

Martin and Nichols[2] reported six cases of bacteremic shock In five, the genitourinary tract was the source of the bacteremia Four of the five had had a surgical or instrumental incident Two of the six expired

Of 29 cases of bacteremia due to gram-negative bacilli studied by Waisbren,[3] the genitourinary tract was the portal of entry in 24 Nineteen of the 29 had either operations or catheterizations, and 15 of the 29 exhibited shock associated with the bacteremia Five of the 29 cases expired

Wise, Shaffer and Spink[4] studied 53 patients with positive blood cultures due to gram-negative bacteria, and in eight of these cases the bacteremia was accompanied by severe hypotension and shock Six of these expired

In the past six months, we have observed five patients in bacteremic shock, three of whom expired

CASE REPORT

This case is representative of the five outlined in table 1 A 77-year old white man was admitted to the medical service of the King County Hospital on February 25 1957 with a vague history of constipation abdominal distension and

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Read at annual meeting of Western Section of American Urological Association Seattle, Wash May 27 30 1957

[1] Hall W H and Gold D Shock associated with bacteremia Arch Int Med **96** 403 1955

[2] Martin W J and Nichols D R Bacteremic shock Proc Staff Meet Mayo Clin **31** 333 340 1956

[3] Waisbren B A Bacteremia due to gram negative bacilli other than the Salmonella Arch Int Med **88** 467 1951

[4] Wise R I Shaffer F M and Spink W W The syndrome of vascular collapse due to gram negative bacteria It management with l norepinephrine and antibiotics J Lab & Clin Med **40** 961 1952

dyspnea of an indeterminate length of time Physical examination revealed the man to be in mild congestive failure, for which he received the indicated therapy Laboratory findings were as follows urinalysis, 15–20 white blood cells per high power field and 20–30 red blood cells per high power field, white blood count, 9000, blood urea nitrogen, 29, electrocardiogram, abnormal, *nonspecific tracing*, chest x-ray, lungs grossly clear, and intravenous pyelogram, essentially normal right collecting system and poor function of the left

The patient was doing well when seen March 13, 1957 by the resident on the genitourinary service because of mild urinary symptoms suggestive of bladder neck obstruction The amount of residual urine was requested and catheterization was performed without difficulty on March 14, 1957 At approximately 3 00 a m on March 15, 1957, a nurse noticed that the patient was flushed, confused, dyspneic and warm to the touch Rectal temperature was 105 2F and the blood pressure was 60/40 An electrocardiogram revealed no evidence of infarction The patient was placed on levarterenol bitartrate, and required amounts as high as 52 cc 0 2 per cent sol /1000 cc to maintain adequate blood pressure Intravenous chloramphenicol and hydrocortisone were also administered The white blood count rose to 27,000, and the blood urea nitrogen rose to 97 Blood and urine cultures revealed coli-aerogenes group, sensitive to tetracycline, chloramphenicol and nitrofurantoin The patient was oliguric and febrile throughout his course, but appeared to improve initially, only to deteriorate and expire on March 19, 1957

Autopsy revealed a hypoplastic left kidney, pyelonephritis of the right kidney and a greatly enlarged, grossly infected prostate gland Death was attributed to a gram-negative septicemia

This case exhibited many characteristic features The onset of the bacteremia was sudden It followed instrumentation by a few hours and was manifest by a shaking chill The chill was followed by a rise in temperature, and, within minutes to a few hours, by an abrupt fall in blood pressure It is important to realize that the hypotension may go unnoticed for many hours because the signs and symptoms of infection do not suggest shock This is of potential danger, because when hypotension persists, the danger of renal ischemia and, ultimately, of renal insufficiency is increased, particularly where there is some underlying renal disease

The exact mechanism of bacteremic shock is not known, but much experimental work has been done on the problem Ebert and Stead[5] were unable to detect any decrease of circulating blood volume in patients in bacteremic shock Borden and his associates[6] suggest that bacterial endotoxins affecting the vascular system and producing vasodilation are partially responsible for the hypotension Penner and Klein[7] believe that the bacterial toxins, rather than affecting the vascular system directly, may do so by causing a central vasomotor paralysis, with resultant shock

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[5] Ebert, R V and Stead, E A Circulatory failure in acute infections J Clin Investig, 20 671–678, 1941

[6] Borden, C W, Hall, W H and Gold, D A study of experimental shock produced by Meningococcus toxin J Lab & Clin Med, 42 787, 1953

[7] Penner, A and Klein, S H The pathogenesis of experimental dysentery intoxication Production of the lesions by cerebral circulation of the toxin J Exp Med, 96 59–69, 1952

TABLE 1

Age	Diagnosis	Source of Bacteremia	Blood Culture	Urine Culture	BUN (Max)	Fever	Therapy	Blood Pressure	Outcome	Autopsy
60	Urethral stricture	Urethral dilatation	Contaminated	Not obtained	212	104	Chloramphenicol, tetracycline, streptomycin, nitrofurantoin, erythromycin, levarterenol bitartrate	40/0	Death	Pulmonary edema, lower nephron nephrosis
78	Urethral stricture	Urethral dilatation	No growth	Proteus	16	104.2	Chloramphenicol, levarterenol bitartrate	80/50	Recovery	
83	Urethral stricture Possible cancer of prostate	Urethral dilatation Needle biopsy of prostate	Achromobacter	Achromobacter Proteus	68	103.2	Chloramphenicol, streptomycin, levarterenol bitartrate	60/0	Recovery	
79	Urethral stricture Possible cancer of prostate	Cystoscopy Needle biopsy of prostate	No growth	Coli aerogenes, hemolytic staphylococcus	35	101	Chloramphenicol, tetracycline, levarterenol bitartrate	10/0	Death	Epidermoid ca & pyelonephritis of left kidney, Staph septicemia, pulmonary emboli
77	B P H	Urethral catheterization	Coli aerogenes	Coli aerogenes	97	105.2	Chloramphenicol, hydrocortisone, levarterenol bitartrate	60/40	Death	Hypoplastic left kidney, right pyelonephritis, acute prostatitis

We, as urologists, should be aware that bacteremic shock is not rare and not uncommonly follows many minor urologic procedures used daily From a review of the literature, and from the cases observed, it is evident that a special type of patient with certain pre-existing conditions is usually involved The majority of the patients are past age 40, have a urinary tract infection, usually a gram-negative organism, and may or may not have pre-existing renal disease The cases presented in this paper, and the vast majority of the patients reviewed in the literature, had surgery or trauma associated with instrumentation, which would allow entrance of the bacteria into the bloodstream Therefore, any patient with a urinary tract infection, and especially one with evidence of renal disease, who requires instrumentation, should be carefully evaluated *If the procedure is not of an emergency nature, treatment prior to instrumentation should be directed toward clearing the infection*

Following instrumentation in the type of patient described, adequate antibacterial therapy is begun empirically after procurement of blood cultures The patient who subsequently exhibits the picture of bacteremic shock must be started on therapy immediately, if morbidity is to be reduced Because these patients may not appear as ill as they are, treatment may be delayed or inadequate, and this can be disastrous All other causes of shock must be considered and ruled out by diagnostic procedures, such as an electrocardiogram, chest x-ray and less common procedures, such as eosinophil count and transaminase determination, if indicated In addition, it is important to consider at the outset that the treatment may be prolonged and require parenteral vasoconstrictor drugs and antibiotics for many days One case[4] has been reported in which the patient recovered after three weeks of intravenous levarterenol bitartrate

Treatment is begun while the various diagnostic procedures are being done, and has two main objectives 1) treatment of the hypotension, and 2) treatment of the infection Treatment of the hypotension must be started immediately, before renal ischemia is of sufficient duration to produce renal damage This would be manifest by persistence of oliguria, or anuria, and elevation of blood urea nitrogen after recovery from shock Bacteremic shock frequently fails to respond to measures such as steroid hormones, whole blood or plasma, which are effective in the management of other hypotensive states *Vasoconstrictor drugs, parenterally administered, should be used early and in adequate amounts Intravenous levarterenol bitartrate has been found to be the most adequate drug for this purpose, but must be used with caution, due to marked local vasoconstriction and possible necrosis* Renal vasoconstriction and reduced renal blood flow are known to result from levarterenol bitartrate administration to normotensive individuals, but Moyer, Morris and Beagley[8] demonstrated an increase in renal blood flow and a decrease in renal vasoconstriction when levarterenol bitartrate was administered to patients in shock One should also use levarterenol bitartrate in sufficient concentration to prevent water intoxication due to excessive intravenous administration Levarterenol bitartrate should be given only with the closest supervision, but it can be given in amounts sufficient to maintain adequate blood pressure. Appropriate and adequate antibiotic therapy is necessary early, because if multiplication of the bacteria is not halted, the endotoxin liberated may be sufficient to cause death, despite ultimate control of the bacteremia. It is known that antibiotics have been unable to control the infection following accidental injection of contaminated blood or infusions. Treatment is started following the collection of blood and urine for culture and sensitivity. All of our cases received chloramphenicol in 0.5 gm. doses every six hours parenterally, and, in addition, received various other combinations of drugs, if indicated. A combination of streptomycin intramuscularly in 1 gm. doses every 12 hours, and one of the tetracycline group, parenterally, every six hours, in doses of 0.75 gm., was used with some success by a group[9] reporting on 137 cases of gram-negative bacteremias. Sensitivity tests may govern a different choice of therapy, but in vitro resistance to an antibiotic does not necessarily mean that the clinical use will be of no value. Treatment should be continued until negative blood cultures are obtained and fever has been absent 72 hours.

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SUMMARY

Bacteremic shock is relatively common in urology following genitourinary tract instrumentation. Adequate treatment of pre-existing infection and avoidance of trauma at the time of instrumentation are important preventative measures. Early recognition and prompt treatment with vasoconstrictor and antibacterial agents will greatly decrease the, otherwise, high mortality.

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ON THE NEPHROSCLEROTIC POTENCY OF PURIFIED ANTERIOR PITUITARY EXTRACTS

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It had long been known that lyophilized anterior pituitary substance and crude anterior pituitary extracts produce nephrosclerosis, polyuria, myocarditis and, occasionally, polyarthritis in rats specially "conditioned" to mineralo-corticoid overdosage by unilateral nephrectomy and a high sodium intake (Selye, 1946) This effect could not be reproduced by lyophilized material or similarly prepared extracts of other organs ACTH was also inactive—at least in amounts that could have been present in our extracts Yet even the most potent nephrotoxic anterior pituitary preparations failed to exert this particular effect in the absence of the adrenals It was consequently assumed that the nephrotoxic and related actions of anterior pituitary extracts are due to some "X-factor," which acts through the adrenal and yet is not ACTH (Selye, 1950) Among all the partially purified anterior pituitary preparations, those containing the highest somatotrophic hormone (STH) content proved to be also most active with regard to nephrotoxic potency, hence it was concluded that the latter property is either due to STH itself or to some factor which cannot be separated from STH by current techniques (Selye and Bois, 1957) Since all available samples of luteotrophic hormone (LTH) share many of the metabolic actions of STH preparations, the question arose whether (in suitably "conditioned" rats) a highly purified LTH could produce nephrosclerosis, myocarditis and polyuria, without stimulating somatic growth

It is the object of this communication to report upon a series of comparative observations concerning the nephrosclerotic and allied actions of highly purified preparations of STH and LTH, which have recently been made available for investigative purposes through the Endocrinology Study Section of the U S National Institutes of Health, Bethesda, Maryland

METHODS

As reported by the distributors, the *characteristics of the STH preparation* (bovine growth hormone, "Somar," Armour) are the following

Primary potency 106 2 per cent ± 15 9 per cent of Armour Standard Relative potency in terms of USP Reference Standard to be reported later

Limits of contamination

Adrenocorticotrophic hormone (ACTH) No activity detectable at doses

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The preparations of LTH (ovine prolactin, "Panlitar," Armour) and STH (bovine growth hormone, "Somar," Armour) have been kindly supplied by the Endocrinology Study Section of the National Institutes of Health, Bethesda, Maryland, while DOC Ac ("Cortate") was supplied by Schering Corporation, Limited, Montreal

of 0.25, 1 and 4 mg per 100 g body weight. Estimate less than 0.06 milliunits (USP) per mg

milliunits (USP) per mg

Thyrotrophic hormone (TTH): Approximately 0.008 USP unit/mg

Follicle-stimulating hormone (FSH): Total doses of 3, 5, and 8 mg injected over a three-day period, fail to augment the increase in ovarian weight induced by 20 units of human chorionic gonadotrophin simultaneously administered to immature female rats

Luteinizing hormone (LH): Total doses of 7.5, 10, and 15 mg injected over a four-day period fail to increase the weight of seminal vesicles, ventral prostate, or testes in immature male rats

Luteotrophic hormone (LTH): Less than 0.1 iu/mg

Vasopressin: Less than 0.01 USP unit/mg

Oxytocin: Less than 0.008 USP unit/mg

The *characteristics of the LTH preparation* (ovine prolactin, "Panlitar" Armour) are:

Primary potency: 20 iu/mg

Estimates of contamination:

Adrenocorticotrophic hormone (ACTH): Less than 0.001 and greater than 0.0005 iu/mg

Thyrotrophic hormone (TTH): Less than 0.0004 USP unit/mg

Follicle-stimulating hormone (FSH): Total doses of 1, 3, 5 and 8 mg injected over a three-day period, failed to potentiate the increase in ovarian weight brought about by 20 units of human chorionic gonadotrophin, simultaneously administered to immature female rats

Luteinizing hormone (LH): A total dose of 10 mg, injected over three days produced no increase in the weight of ventral prostate, and a small, barely significant increase in the weight of the seminal vesicles of immature male rats

Somatotrophic hormone (STH): Less than 1 per cent, greater than 0.1 per cent of the activity of a highly purified bovine growth hormone standard (ratio of potencies estimated 725:1)

Vasopressin: Not more than 0.05 unit/mg

Oxytocin: Not more than 0.05 unit/mg

Two experiments were performed with these hormone preparations. In the first, both STH and LTH were administered at the daily dose of 6 mg (3 mg in 0.2 ml of water subcutaneously twice daily) and in the second at the daily dose of 3 mg (1.5 mg in 0.2 ml of water subcutaneously twice daily).

In the second experimental series we used (as a hormonally inert control substance) a purified *hypertensinogen* preparation at the daily dose of 3 mg or 6 mg. Of this substance we also administered half of the total daily dose in 0.2 ml of water subcutaneously twice daily.

The sensitivity of the partially nephrectomized NaCl-treated rats to nephrotoxic anterior pituitary extracts can be further increased by concurrent treatment with *desoxycorticosterone acetate* (DOC-Ac) as shown by earlier work

(Selye and Bois, 1957) Hence, in the second experiment, half of our animals were sensitized by the daily administration of DOC-Ac (1 mg of microcrystal suspension in 0 2 ml of water once daily subcutaneously)

For the usual "conditioning," all the rats in both experiments were *partially nephrectomized* by ablation of the right kidney, through a lumbar incision, under ether anesthesia, throughout the experiment, they received 1 per cent *NaCl* as their sole drinking fluid, in addition to the "Purina Fox Chow" which served as their sole source of food

As an *indicator of polyuria*, the water intake was measured daily and the mean water consumption during the last ten days (with its standard error) is indicated in the tables

The *blood pressure* was measured with the tail-cuff method once weekly

During the experiment we looked for signs of *polyarthritis* daily, and when present, this was estimated in an arbitrary scale of 1 to 3, on the basis of the swelling, hyperemia and tenderness to touch (1 = just detectable arthritis, 2 = mild arthritis, 3 = severe arthritis) The mean degree of arthritis (calculated by adding all the readings and dividing their sum by the number of animals in each group) is listed in the tables, together with the mean intensity of *nephrosclerosis* and *myocarditis* (likewise estimated in a scale of 1 to 3, based upon histologic study of PAS-stained paraffin sections) The mean *final body weights* (with their standard errors) are also registered as an indication of somatic growth

Both experiments were terminated after 28 days of treatment, at which time the kidneys were fixed in Susa solution for subsequent sectioning

RESULTS

The results of the first experiment are summarized in table 1

Perusal of table 1 clearly indicates that, under the conditions of this experiment, STH greatly stimulated *somatic growth*, whether it was given alone or in combination with LTH, but the latter exerted no growth-stimulating action

Nephrosclerosis and *myocarditis* were either absent or minimal in rats treated with STH alone, or LTH alone, but there was pronounced nephrosclerosis in the animals receiving both these hormone preparations

The *water intake* (and diuresis) was moderately stimulated by STH and LTH alone, but markedly augmented by combined treatment with both these hormones

TABLE 1 *Effect of high doses of STH and LTH alone and in combination, in rats "conditioned" by unilateral nephrectomy and NaCl supplements*

Group	Treatment	Final body weight (gm)	Renal lesions	Cardiac lesions	Water intake (ml /day)	Arthritis	Mortality (%)
I	None	172 ± 3 4	0	0	58 ± 2 5	0	0
II	STH (6 mg)	245 ± 6 7	0 3	0	118 ± 7 1	0	0
III	LTH (6 mg)	178 ± 5 6	0	0 1	93 ± 4 6	0 1	0
IV	STH (6 mg) + LTH (6 mg)	207 ± 11 8	2 3	0 2	158 ± 12 9	1 7	40

Evidence of *polyarthritis* was detectable only in one of the LTH-treated animals, while in rats receiving combined treatment with STH and LTH there was a 50 per cent incidence of arthritis and the lesions were pronounced (edema, swelling, tenderness to touch) and usually affected two or more paws in each animal.

There was no *mortality* in the first three groups but four rats succumbed with marked signs of nephrosclerosis in group 4.

Since in this series LTH alone produced only minor changes, the question arose whether this preparation acted as a sensitizing agent for STH perhaps merely owing to its nonspecific foreign protein effect or whether LTH itself is endowed with nephrosclerotic properties. It was therefore decided to repeat the experiment using only 3 mg/day of STH and LTH, but in an experimental arrangement in which the total amount of foreign protein injected in each group would be the same. Hence 6 mg/day of hypertensinogen was given to the not-hormone-treated controls (group 1) and 3 mg/day of hypertensinogen was injected into the rats receiving 3 mg/day of either STH or LTH (groups 2 and 3) while group 4 received 3 mg/day of STH and 3 mg/day of LTH. Furthermore, since DOC-Ac had been shown to sensitize enormously to the nephrotoxic actions of STH an additional control group received DOC-Ac alone (group 5) or in combination with 3 mg/day each of hypertensinogen (group 6), STH (group 7), or LTH (group 8).

The results of these experiments are summarized in table 2.

It will be seen that under these conditions also, only STH (alone or in combination with LTH) stimulated *somatic growth* significantly.

At this lower dose level, neither STH nor LTH alone produced any *nephro-*

TABLE 2. *Effect of low doses of STH and LTH alone and in combination, in rats "conditioned" either by unilateral nephrectomy and NaCl supplements only or by additional treatment with DOC-Ac*

Group	Treatment	Final body weight (gm.)	Renal lesion	Cardiac lesion	Water intake (ml./day)	Arthritis	Mortality (%)
I	Hypertensinogen (6 mg.)	166 ± 4.7	0	0	46 ± 1.0	0	0
II	Hypertensinogen (3 mg.) + STH (3 mg.)	257 ± 3.4	0	0	94 ± 2.0	0	0
III	Hypertensinogen (3 mg.) + LTH (3 mg.)	183 ± 3.4	0	0	75 ± 2.6	0	0
IV	STH (3 mg.) + LTH (3 mg.)	253 ± 9.3	0.3	0.3	123 ± 3.8	1.4	10
V	DOC-Ac (1 mg.)	149 ± 9.2	0.8	0.2	113 ± 3.5	0	0
VI	Hypertensinogen (3 mg.) + DOC-Ac (1 mg.)	149 ± 5.6	0.3	0.2	98 ± 4.0	0	0
VII	STH (3 mg.) + DOC-Ac (1 mg.)	194 ± 6.7	2.6	2.5	188 ± 8.9	0	20
VIII	LTH (3 mg.) + DOC-Ac (1 mg.)	131 ± 8.2	1.7	2.1	142 ± 3.8	0	20

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* Marked subcutaneous edema and ascites in the majority of the animals of this group.

sclerosis or *myocarditis*, and even combined treatment with the two hormones resulted only in traces of renal or cardiac lesions DOC-Ac alone was moderately effective and concurrent treatment with hypertensinogen certainly did not aggravate this effect, in fact, it appeared to inhibit it slightly although the inhibition was hardly significant On the other hand, in the rats receiving either STH or LTH, in combination with DOC-Ac, the renal and cardiac lesions were extremely pronounced

The *water intake* was likewise unaffected by hypertensinogen alone, and only moderately increased by STH or LTH alone, while pronounced polyuria occurred under the influence of combined treatment with STH or LTH

The diuretic effect of DOC-Ac was not enhanced by hypertensinogen, but it was greatly augmented by both STH and LTH Incidentally, most of the animals of groups 7 and 8 showed pronounced subcutaneous edema and ascites

Polyarthritis again occurred only in the group receiving combined treatment with STH and LTH It should be noted, incidentally, that (just as in our earlier work on the production of polyarthritis with lyophilized anterior pituitary preparations, STH, or DOC-Ac) the joints became affected only towards the end of the second week, and the arthritis gradually diminished after that, both in group 4 of the first experiment and in group 4 of the second experiment

Mortality was noted only in the rats receiving both STH and LTH (group 4), and in those receiving one of these pituitary hormones in combination with DOC-Ac (groups 7 and 8)

The *blood pressure* was subject to great variations even within individual groups so that it did not lend itself to succinct presentation of the mean changes in tabular form This variability is apparently due to the fact that all the nephrotoxic hormones used in these experiments tend to raise the blood pressure, but when the renal damage becomes excessive and the animal is virtually moribund the blood pressure collapses, so that sometimes it can no longer be measured by the tail-cuff method As a result of this, very high and very low blood pressures often occurred in the same group However, it is noteworthy that high blood pressures (140–205 mm Hg or more) occurred only in rats treated with STH, LTH or DOC-Ac, or combinations of these hormones

DISCUSSION

Although our STH and LTH preparations were highly purified and virtually devoid of any known hormonal contaminant, it still remains possible that their effects upon the kidney, heart, joints, blood pressure and water intake may be due to hitherto unidentified hormonal or even non-hormonal substances In any event, it is noteworthy that LTH, which shares some of the effects of STH (e g , some of its actions upon carbohydrate metabolism), exerts nephrotoxic properties, similar to those obtainable with purified STH preparations It remains to be shown whether the latter effect of STH and LTH preparations is due to contamination with a special nephrotoxic principle or whether the effect is an inherent property of the STH and LTH molecule It is noteworthy, however, that the extraordinary aggravation of osteolathyrism (e g , that produced by aminoacetonitrile) that had been obtained with STH preparations could also be reproduced with the sample of LTH used in the present experimental series (Selye, 1957).

SUMMARY

A highly purified preparation of ovine luteotrophic hormone (LTH) shares, with somatotrophic hormone (STH), the property of producing nephrosclerosis, myocarditis, polyuria and polyarthritis in suitably "conditioned" rats.

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sclerosis or *myocarditis*, and even combined treatment with the two hormones resulted only in traces of renal or cardiac lesions DOC-Ac alone was moderately effective and concurrent treatment with hypertensinogen certainly did not aggravate this effect, in fact, it appeared to inhibit it slightly although the inhibition was hardly significant On the other hand, in the rats receiving either STH or LTH, in combination with DOC-Ac, the renal and cardiac lesions were extremely pronounced

The *water intake* was likewise unaffected by hypertensinogen alone, and only moderately increased by STH or LTH alone, while pronounced polyuria occurred under the influence of combined treatment with STH or LTH

The diuretic effect of DOC-Ac was not enhanced by hypertensinogen, but it was greatly augmented by both STH and LTH Incidentally, most of the animals of groups 7 and 8 showed pronounced subcutaneous edema and ascites

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Although our STH and LTH preparations were highly purified and virtually devoid of any known hormonal contaminant, it still remains possible that their effects upon the kidney, heart, joints, blood pressure and water intake may be due to hitherto unidentified hormonal or even non-hormonal substances In any event, it is noteworthy that LTH, which shares some of the effects of STH (e g , some of its actions upon carbohydrate metabolism), exerts nephrotoxic properties, similar to those obtainable with purified STH preparations It remains to be shown whether the latter effect of STH and LTH preparations is due to contamination with a special nephrotoxic principle or whether the effect is an inherent property of the STH and LTH molecule It is noteworthy, however, that the extraordinary aggravation of osteolathyrism (e g , that produced by thelial cytoplasm designated as the "lamina fenestrata", 2) the intermediate layer, the basement membrane proper, designated as the "lamina densa" which is relatively thick and has very small pores, smaller than those of the lamina fenestrata, and 3) the outer layer which is made up of interdigitating terminal processes of the podocytes with spaces between them Hall[2, 3] suggested that the pedicels of the podocytes may be actively variable in width and may control the rate of filtration by changing the free surface of the lamina densa The glomerulus functions as an ultrafilter, letting through colloid-free, cell-free plasma filtrate at a normal rate of about 125 cc per minute Particulate size, more than anything else, governs what passes or does not pass through the glomerular membrane (ultrafilter) This ultrafiltrate, during its passage through the lumina of the renal tubules on its way down to the renal pelvis, where it ultimately becomes urine, is altered by the reabsorptive, excretory, synthetic and detoxifying functions of the tubular epithelium of the kidney The tubular elements of the nephron consist of the primary convoluted tubule, the descending and ascending limbs of Henle's loop, the distal convoluted tubules and the collecting duct of Bellini

The kidney plays at least a fivefold role in maintaining the internal environment of the body in a steady state 1) It eliminates water when an excessive amount of it tends to lower the osmotic pressure of body fluids 2) Certain substances normally present in the blood are excreted by the kidney when their concentration exceeds a certain threshold 3) Substances valuable to the body economy, such as glucose, proteins, amino acids, vitamins and hormones, normally are conserved and selectively reabsorbed as long as their concentration is commensurate with bodily demands and does not exceed the maximal capacity of the renal tubular mass 4) Substances that are useless to the body are excreted by the kidney, no matter what their concentration in the blood may be, and no matter whether they are end-products of metabolism or are introduced into the body from exogenous sources 5) The kidney aids in acid-base balance (a) by formation and substitution of ammonia[4-7] for inorganic base, (b) by excretion of monohydrogen or dihydrogen salts to eliminate or save base, (c) by excretion of variable amounts of inorganic base as bicarbonate and (d) by elimination of fixed acids

In order for the kidneys to function normally and rid the body efficiently of its endogenous and exogenous metabolic wastes, certain major physiologic conditions must be fulfilled Among the factors which contribute to normal renal function are the following 1) total volume of circulating blood, 2) rate and quantity of blood passing through the kidney, 3) hydrostatic and colloid osmotic pressure of the blood, 4) intrarenal, luminal and capsular pressures and 5) the

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[4] Shannon J A The renal excretion of creatinine in man J Clin Invest , **14** 403–410, 1935

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PHYSIOLOGIC BASIS FOR ANURIA AND PROTEINURIA

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For a better understanding of the various mechanisms involved in the genesis of anuria and proteinuria, it is important that the advances in the field of renal physiology be presented concisely and clearly with special emphasis on the clinical applications from the recent advances The aberrations in renal function are the basis for the clinical manifestations encountered in patients with kidney disease Both the physician and the patient would be far better off if the newer findings in renal physiology were clearly understood and their important role in the genesis of kidney disease was carefully assessed and appreciated

FUNCTIONS OF THE KIDNEY

The kidney is the organ on which depends the dynamic stability of the internal environment of the body and the subsequent maintenance of a steady state The kidney is mainly responsible for the regulation and maintenance of fluid, electrolyte, osmotic and acid-base balance This is not to deny that other organs, such as the lungs, gastrointestinal tract, skin and liver, contribute to that regulation and maintenance Homer Smith[1] aptly wrote, "It is no exaggeration to say that the composition of the blood is determined not by what the mouth ingests but by what the kidneys keep They are the master chemists of our internal environment " Urine is a by-product of the regulatory functions of the kidney

In these regulatory functions, as well as in the ultimate production of urine, both the glomeruli and the tubules take part The nephron is the functional unit of the kidney It is made up of the glomerulus, which consists of an afferent and a smaller efferent arteriole, together with a tuft of capillaries which invaginate, and become ensheathed by, Bowman's capsule At its entry into the glomerulus, the afferent arteriole expands and gives rise to several trunks which ramify into smaller branches (capillaries) Each of these trunks with its capillary ramifications, which anastomose freely and form a network of fine vessels, constitutes a glomerular lobule[2, 3]

The filtration membrane constitutes the glomerular wall, it separates the blood from the space within Bowman's capsule Studies with the electron microscope indicate that the complete filtration membrane is composed of three layers 1) the internal layer which is the cribriform attenuated portion of endo-

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[1] Smith, H W Studies in the Physiology of the Kidney Lawrence, Kansas University Extension Division, University of Kansas, 1939, 106 pp

[2] Hall C V Studies of Normal Glomerular Structure by Electron Microscopy [Including Discussion] In Proceedings of Fifth Annual Conference on the Nephrotic Syndrome held at the Children's Hospital, Philadelphia, Pennsylvania, November 5–7, 1953 New York The National Nephrosis Foundation, Inc , 1953, pp 1–39

[3] Hall, C V Further Studies of the Normal Structure of the Renal Glomerulus [Including Discussion] In Proceedings of Sixth Annual Conference on the Nephrotic Syndrome held at Western Reserve University School of Medicine, Cleveland, Ohio November 5–6, 1954 New York The National Nephrosis Foundation, Inc 1955, pp 1–39

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FUNCTIONS OF THE KIDNEY

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In these regulatory functions, as well as in the ultimate production of urine, both the glomeruli and the tubules take part The nephron is the functional unit of the kidney It is made up of the glomerulus, which consists of an afferent and a smaller efferent arteriole, together with a tuft of capillaries which invaginate, and become ensheathed by, Bowman's capsule At its entry into the glomerulus, the afferent arteriole expands and gives rise to several trunks which ramify into smaller branches (capillaries) Each of these trunks with its capillary ramifications, which anastomose freely and form a network of fine vessels, constitutes a glomerular lobule[2, 3]

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1) The nearness of the kidneys to the aorta makes the course of the renal artery very short and the loss in pressure minimal

2) On entry into the kidney the renal artery abruptly and successively breaks up into several interlobar arcuate and interlobular arteries and finally into the afferent arterioles

3) The diameter of the efferent arteriole is generally half that of the afferent

4) Not only does the afferent arteriole break up into the first set of capillaries in the glomerulus (which reunite to form the efferent arteriole), but furthermore the efferent arteriole breaks up into another set of capillaries around the various elements of the tortuous tubules

5) The blood in the basket of capillaries enmeshed around the tubules is highly viscous because it emerges from the glomerular capillaries into the efferent arteriole after it has lost a huge filtrate of colloid-free, cell-free plasma This second network of small vessels and the concentrated, highly viscous blood within them contribute significantly to the high resistance beyond the glomeruli and the consequent high pressure within the glomerular tuft of capillaries

In summary, it can be said that the kidneys manufacture urine as a by-product of their major functions the regulation and maintenance of water, electrolyte, osmotic and acid-base balance The 2,000,000 or more nephrons present in the kidneys as functional units are made up of glomeruli and tubules,[9, 10] the glomeruli function as ultrafilters and the tubules perform the functions of selective reabsorption, secretion or excretion synthesis and detoxification, depending on the demands of the body economy and the status of the internal environment

RENAL RESERVE

In addition to the amazing regenerative capacity of renal epithelium and the possibility of intermittent glomerular activity, the kidney has a certain functional reserve It is important to know how much renal tissue can be destroyed before renal impairment becomes apparent Pearce[11] and also Allen Bollman and Mann[12] demonstrated that removal of 50 to 66 per cent of the renal tissue from the dog produces no detectable change in urinary volume or in urinary nitrogen When two thirds of the renal tissue is lost the mean clearance values attain the lowest ranges of normal[13] The amount of functioning renal tissue must be reduced to about a third of normal before the blood value of various metabolites normally excreted by the kidney begins to rise[14-16] It has been reported that

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morphologic status of the glomeruli and tubules The kidneys are richly supplied with blood They receive approximately 1,300 cc every minute or practically a fourth of the total cardiac output

Under the ordinary conditions of everyday life the rate of formation of urine is far from constant The factors that have been mentioned greatly influence formation of urine Some affect filtration, others influence reabsorption or secretion or both Increasing the rate of filtration, reducing the rate of reabsorption, or a combination of these increases production of urine There is some evidence that the number of patent or active glomeruli varies under the influence of chemical and nervous agents Some authorities have stated that glomerular activity of the mammalian kidney is not intermittent However, convincing evidence is accumulating in favor of intermittent activity of the glomeruli

Changes in pressure within the glomerular vessels influence the rate of filtration Dilatation of the afferent arteriole or constriction of the efferent arteriole causes a rise of pressure in the glomerular capillaries and favors filtration The volume of blood which flows through the glomeruli and the rate of flow exert important influences on the rate of filtration Reduction of hydrostatic pressure and renal ischemia resulting from shock, hemorrhage or any condition that drastically reduces the blood volume and blood pressure are accompanied by severe reduction in glomerular filtration

The osmotic pressure of the filtrate, as well as its volume and the rate of its passage through the lumina of the tubules, influences reabsorption These, therefore, are important determinants of the volume and concentration of urine ultimately produced

The interplay of intrarenal pressures can be expressed in an equation where effective filtration pressure is represented by EFP, glomerular hydrostatic blood pressure by GBP, colloid osmotic pressure of the blood by COP, and the pressure within Bowman's capsular space and the lumen of the tubule (the capsular pressure) by CP Hence,

$$\text{EFP} = \text{GBP} - (\text{COP} + \text{CP})$$

Substitution of the figures in millimeters of mercury for the various components causes this formula to read as follows

$$40 = 75 - (25 + 10)$$

This shows that for filtration to occur through the glomeruli, the hydrostatic pressure within the glomerular tuft of capillaries must definitely exceed the sum of the colloid osmotic pressure of the blood and the pressure within the renal capsule and lumen of the tubules

Whereas in other parts of the body the blood pressure is considered to average about 30 mm of mercury on the arterial end of the capillary and about 15 mm on the venous end, the hydrostatic blood pressure in the glomerular capillaries was found to range from 54 to 70 per cent[8] of that in the aorta Thus, in mammals the hydrostatic pressure in the glomerular capillaries is about 75 mm of mercury

Several anatomic and physiologic factors contribute to the development of a high capillary blood pressure within the glomeruli

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in the distal convoluted tubules and the ascending limb of Henle's loop, more will be said of it later

Due to dehydration The oliguria which accompanies severe dehydration is initially a physiologic response One of the major functions of the kidney is maintenance of fluid balance To perform this function efficiently under conditions of severe dehydration, the kidney is frugal with the scanty fluids available within the body Consequently, extremely small amounts of urine are eliminated by the normal kidney until fluids are again available This small volume of urine is of a high specific gravity Usually, what has been described occurs if a patient has normally functioning kidneys but becomes severely dehydrated If the specific gravity is low in spite of the scanty volume, the kidneys are not normal

When water and electrolytes are lost because of severe diarrhea, excessive vomiting, profuse sweating, or a combination of these, and neither water nor electrolyte is administered to replenish the losses, anuria is to be expected This is a process physiologically provided to safeguard against fatal depletion of body water The process becomes dangerous only when it is overlooked and inspissation of body tissues leads to abnormal metabolism and severe damage of vital organs, including the kidneys themselves Severe depletion of electrolytes and extreme changes in pH, if of considerable duration, may produce renal damage

If severe dehydration is recognized early and the lost fluids and electrolytes are judiciously replaced, normal kidneys easily can handle the situation These are the clear-cut cases of clinically encountered anuria and the patients are cured permanently by judicious treatment of their dehydration The return of urinary volume to normal after body water and electrolytes have been replenished is proof of renal integrity Therefore, the problem in the presence of anuria of dehydration is one of fluid and electrolyte balance, it is not a renal problem

Due to circulatory disturbances The anuria resulting from circulatory disturbances usually is manifested in the presence of 1) shock with peripheral circulatory collapse, 2) prolonged fall in blood pressure, 3) reduced blood volume, 4) reduced renal blood flow and 5) renal ischemia Anuria from these causes may appear postoperatively or after severe trauma to the body such as is sustained in some severely traumatizing accidents In such cases, the kidneys may or may not be initially normal Moreover, if the circulatory disturbance continues, initially normal kidneys may not remain normal Block, Mann, Bennett and I[20] demonstrated experimentally that prolonged circulatory collapse with accompanying hypotension, caused by hemorrhage, produces complete anuria and can cause severe, irreversible injury to previously normal kidneys Penner and Bernheim[21] have shown that prolonged vasomotor collapse is a basic cause of the development of bilateral cortical necrosis of the kidney

During tedious surgical procedures especially if the operation is extensive, the loss of blood, the injury to tissues, the prolonged anesthesia, the dehydration from sweating, and preoperative anxiety can cause severe hypotension and more than three fourths of the renal substance must be destroyed before dogs die from renal insufficiency [17] [19]

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Several mechanisms are called on to maintain renal function in states in which parts of the renal tissue become functionless because of inflammatory or degenerative disturbances For one thing, the nephrons which remain healthy compensate for the destroyed nephrons by undergoing hypertrophy After microscopic examination of specimens from severely damaged renal tissue, pathologists often report hypertrophy of healthy nephrons Some have called this "work hypertrophy"

Another means of renal reserve is an interplay of physiologic mechanisms which leads to increased filtration pressure and reduced reabsorption The high blood pressure in some types of renal disease increases filtration and the large volumes of dilute urine encountered in some cases may be a compensation for the inability of a diseased kidney to concentrate A much larger volume of urine is eliminated to rid the body of the usual quantity of solids

However, if the quantity of urine eliminated has a consistently fixed specific gravity in the neighborhood of 1 010 at a time when the patient's intake of fluid is restricted, the inference is that the kidneys are unable to concentrate The specific gravity of such urine (1 010), which is the same as that of the glomerular filtrate, indicates that the renal parenchyma is so severely damaged that it is not capable of doing osmotic work Urine of this density is glomerular filtrate unaltered and indicates the existence of an ominous state of the kidneys Normal kidneys can concentrate urine to a specific gravity of 1 035 or more when the intake of fluid is restricted and the diet is high in protein They also can dilute urine to a specific gravity of 1 000 when much water is administered In other words, a wide range of ability to concentrate and dilute is an index of the presence of healthy, versatile renal parenchyma

ANURIA

The foregoing salient anatomic and physiologic features underlie the types of anuria that are encountered clinically From the point of view of aberrations in renal physiology, anuria can occur in the presence of any one of the following states when 1) dehydration is the major factor, 2) circulatory disturbances, including glomerular damage, are of sufficient magnitude, 3) degenerative changes in the epithelium of the renal tubules are extensive, and 4) intrarenal and postrenal obstructive conditions involve both kidneys It is essential to keep in mind that more than one mechanism may, and that two or more mechanisms usually do, participate in causing urinary suppression This is especially true in certain oliguric states grouped under the term "lower nephron nephrosis" This term originates from the erroneous concept that the lesion is localized only from the edges of the epithelial defect The epithelial defects are ultimately covered by the proliferation of cells from the islets of persisting epithelium scattered along the denuded tubule After epithelial repair, cellular maturation and rearrangement follow with gradual re-establishment of lining membrane, lumina and function of regenerated tubules *Even if the glomerular filtrate is of* normal volume and concentration, in its passage through the tortuous, degenerated, desquamated tubules it is practically completely reabsorbed into the adjacent capillaries The outcome is severe anuria of the degenerative type

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The anuria may be very severe and uremia may be impending, but the condition should not be hastily pronounced hopeless The regenerative capacity of the renal epithelium, as has been said, is great In cases of uremia with anuria, urinary volume sometimes begins to rise gradually at the end of 10 days or 2 weeks By correlating experimental evidence with clinical experience, it easily can be understood that the rise in urinary volume coincides with the time of successful re-epithelialization when sufficient renal epithelium has recovered and partially but effectively has replaced the physiologic barrier that was lost in the process of severe degeneration Mercurial types of nephrosis are among the good examples of toxic or degenerative anuria

Due to obstruction of urinary passages Another type of anuria known clinically is the obstructive type The renal tubules could be blocked and dilated 1) by compression of renal tissue by severe interstitial edema, 2) by pigments from destroyed hemoglobin or myoglobin, 3) by crystals of sulfonamide or other drugs, 4) by debris formed by desquamation and necrosis, 5) by bilateral compression of the ureters and renal pelvis exerted by extensive regional tumors, and 6) by partial urethral obstruction In the presence of severe dehydration or of circulatory collapse with shock, pigment nephropathies are easily initiated and may become extensive or even serious

When the filtrate in the lumina of the tubules is prevented from proceeding along them down to the renal pelvis, the increase of pressure reduces filtration, and the delay in passage of the filtrate enhances reabsorption, both of which initially encourage oliguria but ultimately may bring about complete anuria If these obstructive factors cannot be, or are not, relieved, the anuria terminates in uremia

Bywaters and others[24-28] reported renal lesions in cases in which patients died of anuria following crushing injuries The "crush syndrome" consists of shock, azotemia, low blood pressure, uremia and anuria Lucké[29] has designated the renal pathologic picture of the crush syndrome, "lower nephron nephrosis" be-

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[29] Lucké Balduin Lower nephron nephrosis (the renal lesions of the crush syndrome of burns transfusions and other *conditions affecting* the lower segments of the nephrons) Mil Surg 99 371–396 1946

anuria Postoperative anuria is of common occurrence The hypotension which is the immediate result of reduced blood volume, hemoconcentration and vasodilatation causes postoperative anuria even in the presence of healthy kidneys This condition usually is accompanied by reduced cardiac output, diminished renal blood flow and renal ischemia Under conditions of hypotension and reduced renal blood flow, the effective filtration pressure is insufficient for elaboration of significant quantities of glomerular filtrate In the presence of hemoconcentration most of the filtrate is reabsorbed by the renal tubular epithelium, and anuria is the outcome If postoperative circulatory collapse (shock) is combated early by intravenous administration of compatible fresh blood and an appropriate concentration and quantity of electrolytes, the kidneys will remain normal, and the anuria soon will be alleviated But if the postoperative state of shock endures, renal damage may set in and the anuria may become more severe

Retention of nitrogenous constituents is ushered in by their high concentration in the blood A few cases in which this occurs may terminate in uremia if the state of shock and hypotension are not relieved,[20] but a fairly high percentage of the patients recover The regenerative capacity of the kidney is encouraging, within 24 hours after severe damage to the renal parenchyma, mitotic figures[22] easily can be demonstrated in various stages throughout the tubular epithelium Replacement of destroyed renal parenchyma is surprisingly fast, especially if the therapeutic management does not overtax the renal epithelium which is struggling to rebuild the desquamated tubules by replacement and substitution of new renal epithelial cells

Due to degeneration of renal tubules In the light of a clear understanding of renal hemodynamics the explanation of degenerative anuria is not difficult The degenerative type of anuria implies loss of the epithelial lining of the renal tubules Destruction of the lining epithelium means elimination of the physiologic barrier between the filtrate in the lumen and the concentrated blood in the capillary network around the tubules In the absence of selective activity of renal epithelium, the filtrate in the lumina of the desquamated tubules is voraciously reabsorbed by *the osmotic activity of the highly concentrated blood* surrounding it Furthermore, Oliver[23] has demonstrated morphologically that disruption of the continuity of the tubular portion of the nephron including dissolution of its basement membrane could occur This phenomenon is termed "tubulorhexis" and may involve short segments or long stretches of the tubules Under such conditions the filtrate escapes into the interstitial spaces and comes in direct contact with the peritubular plexus of vessels containing highly viscous blood Hypertrophy and hyperplasia of the cellular elements that have escaped damage can be demonstrated in nephrons in which only some zones are destroyed This epithelial proliferation throws the tubule into a series of irregular, thickened coils which add to its functional capacity in compensating for the destroyed zones The new cells are seen extending inward over the bare basement membrane ureters or prostate gland initiate reflex anuria, but it is doubtful whether such transient reflex stimulation without persistent irritation can cause lasting anuria

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[22] Block, M A , Wakim, K G , Grindlay, J H and Mann, F C Factors contributing to renal enlargement after ureteroduodenostomy and contralateral nephrectomy Surgery, 34 211-226, 1953

[23] Oliver Jean Correlations of structure and function and mechanisms of recovery in acute tubular necrosis Am J Med 15 535-557, 1953

By continuous electric stimulation[35] of the renal nerves Block, Mann and I were able to produce sufficient renal vasoconstriction to effect marked reduction in renal blood flow for only a few minutes Blood flow through the kidney was much reduced and clearances of creatinine and para-aminohippurate (PAH) as well as extraction ratios of PAH decreased precipitously at the beginning of stimulation of the renal nerves However, all values returned practically to normal within 1 to 2 hours despite continuance of stimulation of renal nerves[36] Anuria or oliguria of more than 70 minutes' duration could not be produced by stimulation of the renal nerves Our findings, therefore, do not support the view that prolonged anuria or oliguria is attributable to renal vasoconstriction mediated by the renal nerves Reflex renal vasoconstriction by excitation of the sciatic nerves, sudden clamping of the extremities, or tracheal occlusion could not be maintained any longer than that produced by direct stimulation of the renal nerves

THE MECHANISM OF PROTEINURIA

Normal urine has long been considered to be protein-free, and the presence of protein in the urine has been considered indicative of renal disease The demonstration of absence of protein from the glomerular filtrate in frogs by Wearn and Richards[37] strengthened these concepts The idea that normal urine is protein-free has been challenged by many investigators Mörner[38] demonstrated the presence of 22 to 78 mg of protein per liter of urine Gunton and Burton[39] found the mean concentration to be 3 7 mg per 100 cc The mean value for urinary output of protein per 24 hours was found to be 39 mg (30 5 to 49 6) by Rigas and Heller[40] Comparison of urinary with serum proteins by electrophoretic analysis reveals the presence of the same components in each Relatively more globulin was found in urine than serum and the albumin-globulin ratio for urine was the reverse of that in serum The greater proportion of globulin in the urine was attributed to greater tubular reabsorption of albumin After producing renal damage in fish Bieter found that proteinuria developed in those whose kidneys had glomeruli but not in those whose kidneys were aglomerular[41] Addis administered rat serum to rats of the same strain and produced proteinuria without cause he found *only* the lower nephrons affected Lucké expressed the belief that the degradation products of hemoglobin and myoglobin, the products of breakdown of tissue, shock, and alteration of the blood and body fluids all acted in combination to bring about renal ischemia and anuria Bywaters and also Mallory[30] suggested that true "lower nephron nephrosis" is associated with either muscle injury or intravascular hemolysis or both They expressed the belief that precipitation of pigment in the distal portions of the tubules and collecting ducts is a major cause of the anuria On the other hand, Peters[31] attributed the anuria of the crush syndrome to the increased interstitial pressure in the kidneys

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[35] Block M A , Wakim K G and Mann, F C Circulation through kidney during stimulation of the renal nerves Am J Physiol **169** 659–669, 1952

[36] Block M A Wakim K G and Mann F C Renal function during stimulation of renal nerves Am J Physiol **169** 670–677 1952

[37] Wearn J T and Richards A N Observations on the composition of glomerular urine with particular reference to the problem of reabsorption in the renal tubules Am J Physiol **71** 209–227 1924

[38] Mörner, K A H Untersuchungen über die Proteïnstoffe und die eiweissfällenden Substanzen des normalen Menschenharns Skandinav Arch f Physiol , **6** 332–437, 1895

[39] Gunton R and Burton, A C On the concentration of protein in samples of normal urine measured by its surface activity J Clin Invest **26** 892–898, 1947

[40] Rigas, D A and Heller, C G The amount and nature of urinary proteins in normal human subjects J Clin Invest **30** 853–861 1951

[41] Bieter R N Albuminuria in glomerular and aglomerular fish J Pharmacol & Exper Therap **43** 407–412 1931

Block, Mann, Bennett and I noted in our studies[20] that certain parts of renal lesions produced by prolonged hypotension resembled microscopically those found in association with so-called lower nephron nephrosis However, the severest damage was to the proximal tubules Casts were more prominent in the lower nephron and collecting tubules, which frequently had undergone degenerative changes The casts consisted of hyaline material which evidently originated from proximal tubules, for when these tubules degenerated, the cells assumed a hyaline appearance Previous investigators considered the hyaline casts in the distal tubules to have originated from degenerating proximal tubules[32, 33] The predominant disturbance in either case is destruction of tubular cells, degeneration is present in all segments of the tubules and whether or not the damage is localized in any one segment of a tubule is not important Smith[34] summarized the injury of acute renal failure as widespread, scattered tubular damage affecting *any or all segments of the nephron*

The concept of anuria from blockage of the renal tubules by necrotic debris is *the basis for advocating intravenous administration of large amounts of fluids* to dilute, dissolve and flush out the obstructing material This indiscriminate internal bathing of anuric patients may have helped the few who were severely dehydrated and badly needed the administered fluids for their relatively healthy kidneys to work on, but it certainly has drowned many a patient in his own fluid, in the sense that it has led to pulmonary edema and failure of the left side of the heart from overfilling the circulatory system, overtaxing the myocardium and overloading the tissues with excessive amounts of both salt and water

Reflex anuria Reference often has been made in the urologic literature to reflex anuria *It is presumed to result from catheterization*, or operative manipulation, of organs of the urogenital system Occasionally operations on the kidneys, plasma proteins from the glomerular filtrate Sellers and co-workers[45] have demonstrated that urinary proteins have the same electrophoretic and solubility characteristics as the alpha and beta globulins of serum If these large molecules are able to pass through the glomerular membranes, the smaller ones (albumin) certainly should The plasma proteins are constantly passed in various quantities into the filtrate through the glomeruli and at the same time are continuously reabsorbed by the epithelial cells lining the renal tubules and are eventually returned to the bloodstream after some intracellular modification

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[30] Mallory, T B Hemoglobinuric nephrosis in traumatic shock Am J Clin Path, **17** 427–443, 1947

[31] Peters J T Oliguria and anuria due to increased intrarenal pressure Ann Int Med, **23** 221–236, 1945

[32] Oliver, Jean Architecture of the Kidney in Chronic Bright's Disease New York Paul B Hoeber, Inc, *1939*, 256 pp

[33] Quensel, Ulrik Untersuchungen über die Morphologie des organisierten Harnsediments bei Krankheiten der Nieren und der Harnwege und über die Entstehung der Harnzylinder Nord med Arkiv **50** [II] 319–662, 1917–1918

[34] Smith, H W The Kidney Structure and Function in Health and Disease New York Oxford University Press 1951, 1049 pp

The glomerular filtrate in normal adult men amounts to about 180 liters per 24 hours It contains, as variously reported, amounts ranging from 10 to 200 mg of protein per 100 ml of filtrate Therefore, from 18 to 360 gm of plasma proteins pass through the glomeruli with the filtrate daily, and since practically none of that is normally present in the urine the renal tubules must reabsorb that quantity of proteins daily Oliver expressed the belief that whenever the capacity of the tubular cells to absorb proteins from the filtrate in the lumen of the tubules is exceeded by the amount or the nature of the protein, an accessory mechanism of droplet formation shows up This mechanism is an intracellular process in which cytoplasmic elements, the mitochondria with their enzymes, and the absorbed protein unite to form droplets Oliver considered these droplets as foci of metabolic activity rather than cytologic structures of hyaline[49] These droplets are highly active centers of protein metabolism

In the light of the evidence presented in literature it can be stated that plasma proteins of varying amounts, depending on the status of the glomeruli, constantly pass through the glomeruli with the glomerular filtrate into the tubules The epithelial cells lining the tubules, on the other hand, constantly reabsorb these proteins In a state of normalcy the kidneys manipulate the plasma proteins in such a manner that none is detectable in the urine by the ordinary clinical tests Therefore, for all practical purposes it can be said that normally there is no protein in the urine However, in disease states when the permeability of the glomeruli is increased plasma proteins leak through into the glomerular filtrate in amounts beyond the capacity of the tubular cell mass to reabsorb them completely, consequently, a state of proteinuria ensues Abnormal permeability of the glomeruli exceeding the capacity of the tubular epithelium to reabsorb the filtered proteins or disease of the epithelial cells of the renal tubules reducing or annulling their ability to reabsorb proteins from the glomerular filtrate is the basic cause of the genuine proteinurias clinically encountered

Chinard and co-workers[50] came to the conclusion that proteinuria results from increased permeability of the glomerular capillary to proteins rather than solely from a decrease in the reabsorption of proteins by the tubules renal damage The proteinuria was attributed to increased concentration of proteins in the plasma [42] Similar findings were obtained in dogs given dog plasma[43] and on patients with cirrhosis of the liver after several intravenous injections of human serum albumin [44] These various findings provided support for the concept that glomerular filtration is the mechanism for the appearance of protein in the urine

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[45] Sellers A L Roberts Sidney Rask Irene Smith, Stephen, III Marmorston, Jessie and Goodman H C An electrophoretic study of urinary protein in the rat J Exper Med 95 465–472 1952

[49] Oliver Jean MacDowell Muriel and Lee Y C Cellular mechanisms of protein metabolism in the nephron I The structural aspects of proteinuria, tubular absorption droplet formation and the disposal of proteins J Exper Med 99 589–604, 1954

[50] Chinard F P Lauson H D Eder H A Greif R L and Hiller A A study of the mechanism of proteinuria in patients with the nephrotic syndrome J Clin Invest 33 621–628 1954

HYPOTHESES REGARDING MECHANISM OF PROTEINURIA

Over the years several hypotheses have been developed to explain the mechanism of proteinuria They can be stated concisely as follows

1) Abnormal glomerular capillaries leak plasma proteins, but the tubules are passive in that matter

2) Diseased glomerular capillaries leak excess plasma proteins far beyond the capacity of the tubules to reabsorb them completely

3) Tubular epithelium secretes protein

4) Altered plasma proteins (dysproteinemia) pass through glomerular membranes

5) Interference with renal venous return increased glomerular permeability to protein

6) Chyle draining into collecting tubules or calyces carries protein with it

In assessing these hypotheses I shall present in the light of available recent evidence a few facts which may help the reader in looking into more detailed information in the support of the most plausible hypothesis

Leakage of plasma proteins through abnormally permeable glomerular capillaries is the basic cause for appearance of protein in the glomerular filtrate However, the epithelial cells of the renal tubules are not passive in that matter Overwhelming evidence has accumulated in recent years in support of an important role played by the epithelium of the renal tubules in the reabsorption of proteins from the glomerular filtrate In an extensive review Rather[45] presented convincing evidence that the cells lining the proximal convoluted tubules can reabsorb protein from the glomerular filtrate The dye T-1824 forms a stable blue complex with plasma proteins The injection of the dye T-1824 labels the plasma proteins to which this dye is attached, absorbed or combined The dye with the plasma proteins it tags is found concentrated in the cells of the proximal convoluted tubules [46] [47] This is good evidence for tubular reabsorption of the

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[42] Addis, T The mechanism of proteinuria Proc Nat Acad Sc, 35 194–198, 1949

[43] Terry, Roger, Hawkins, D R, Church, E H and Whipple, G H Proteinuria related to hyperproteinemia in dogs following plasma given parenterally J Exper Med, 87 561–573, 1948

[44] Thorn, G W, Armstrong, S H, Jr and Davenport, V D Chemical, clinical, and immunological studies on the products of human plasma fractionation XXXI The use of salt-poor concentrated human serum albumin solution in the treatment of hepatic cirrhosis J Clin Invest, 25 304–323, 1946

[45] Rather, L J Filtration, resorption and excretion of protein by the kidney Medicine, 31 357–380, 1952

[46] Dock, William Proteinuria and the associated renal changes New Eng J Med, 227 633–636, 1942

[47] Gilson, S B Studies on proteinuria in the rat Proc Soc Exper Biol & Med, 72 608–613, 1949

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A CLINICAL COMPARISON AND ANALYSIS OF RADIOACTIVE DIODRAST, HYPAQUE, MIOKON AND UROKON RENOGRAMS AS TESTS OF KIDNEY FUNCTION

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Previous studies with diodrast-I^{131} have indicated its clinical usefulness in an external method of measuring individual renal function (The Radioactive Diodrast Renogram) [1-3] Characteristic and reproducible tracings representing the changing levels of radioactivity over the kidney areas are recorded continuously, following the intravenous injection of tracer doses of this radioisotope Distinctive renograms were found for the normal functioning kidney as well as a variety of renal and upper urinary tract disorders Furthermore, the tracing (renogram) has three components which are qualitative indices of 1) renal vascular capacity, 2) tubular cell function, and 3) ability of the kidney and ureter to evacuate urine

In order to evaluate other contrast media now commonly used for urography, as test agents for renal function, the radioactive renogram test was performed in a series of patients utilizing I^{131}-tagged hypaque and miokon Urokon-I^{131} has been tested and reported previously [1, 2] and was found unsatisfactory as a test agent for measuring renal tubular function externally Rather, the radioactive *urokon* renogram portrays a pattern of blood clearance only in all individuals tested, because in tracer doses it is excreted slowly by glomerular filtration

MATERIALS AND EQUIPMENT

Hypaque,* miokon† and urokon‡ were tagged with I^{131} by ion exchange and diodrast§ by synthesis in concentrations of 50–100 microcuries per milligram of medium ‖ The test dose varied from 5 to 20 microcuries (1 μc per 5 kilograms of body weight)

The test equipment consisted of dual units, each composed of a collimated gamma ray scintillation detector, a rate meter and an Esterline-Angus recorder (one for each kidney)

Accepted for publication October 8, 1957

[1] Taplin G V, Meredith O M, Kade H and Winter, C C The radioisotope renogram J Lab & Clin Med 48 886–901, 1956

[2] Winter C C A clinical study of new renal function test The radioactive diodrast renogram J Urol 76 182–196 1956

[3] Winter, C C Unilateral renal disease and hypertension, use of radioactive diodrast renogram as screening test J Urol, 78 107–116 1957

* Hypaque is the trade name for sodium diatrizoate (Winthrop Laboratories, New York)

† Miokon is the trade name for sodium diprotiozoate (Mallinkrodt Chemical Works, St Louis, Mo)

‡ Urokon is the trade name for sodium acetrizoate (Mallinkrodt Chemical Works, St Louis Mo)

§ Diodrast is the trade name for iodopyracet (Winthrop Laboratories, New York)

‖ All radioactive agents were furnished by Abbott Laboratories, Oak Ridge, Tenn

As the other hypotheses have insufficient evidence in their support, I will enumerate a few facts that render two of them untenable

The idea that diseased tubular cells secrete protein into the lumen of the renal tubules requires that protein be present normally in the interstitial fluid within the kidney and that permeability of the peritubular capillaries be increased There is no evidence in support of this hypothesis Proteinuria is minimal or absent in cases of pyelonephritis when the peritubular capillaries are involved in the inflammatory process The histologic demonstration of protein coagulum in Bowman's capsular space is strong evidence against tubular secretion of protein

The concept of dysproteinemia has been advanced suggesting that the plasma proteins are so altered that they pass through the glomeruli into the filtrate more readily than normal plasma proteins Experiments by my colleagues and me do not support the idea of dysproteinemia We produced experimental nephrosis in rats by the use of antirat kidney rabbit serum (nephrotoxic serum), and at the peak of albuminuria we completely replaced the blood of normal litter mates by total transfusion of blood from the nephrotic rats In spite of having had their circulatory blood volume replenished by nephrotic blood, the normal rats showed no abnormal or significant albuminuria for several days If the severe proteinuria in the nephrotic rat was due to altered plasma proteins, the normal litter mate should have exhibited marked proteinuria after total replacement of his blood by nephrotic blood Bradley and Tyson[51] found no convincing evidence in support of dysproteinemia as a cause for proteinuria

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[51] Bradley, S E and Tyson, C J The "nephrotic syndrome" New Eng J Med, 238 223-227, 1948

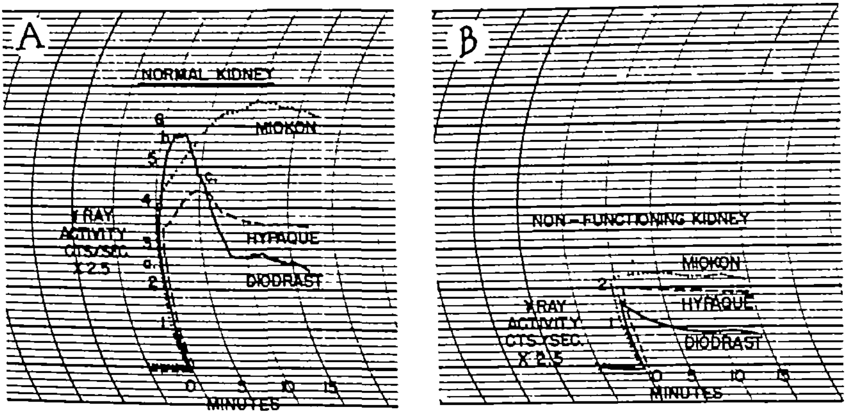


Fig 2 *A*, comparative radioisotope renograms of a normal kidney are shown Tracing is composed of three segments a) height of initial spike is indicative of vascular supply to kidney, b) character of secondary rise is an index of tubular cell function, and c) degree of terminal decline in tracing represents ability of kidney and ureter to evacuate urine *B*, comparative renograms of a non functioning kidney are shown Note lack of secondary rise after abbreviated initial spike

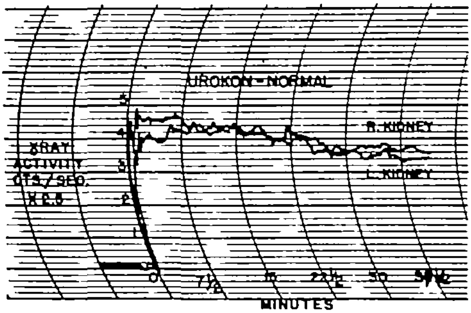


Fig 3 Radioactive urokon renogram does not have a secondary rise, indicating absence of active tubular cell function Slow descent of tracing represents passive glomerular filtration

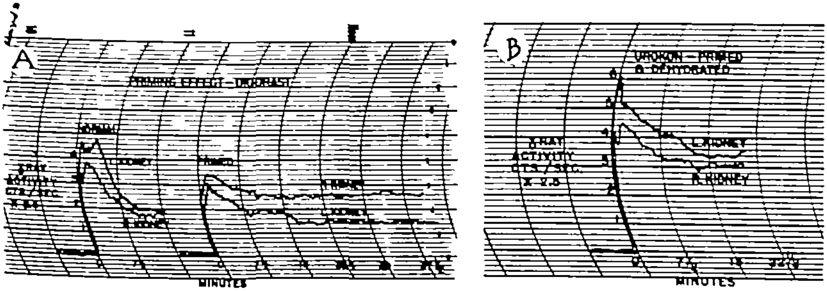


Fig 4 *A*, priming kidney with large quantities of diodrast by intravenous injection causes radioactive diodrast to be secreted more slowly and thus tracing descends more slowly *B*, priming kidney with urokon results in more rapid excretion of urokon I^{131}

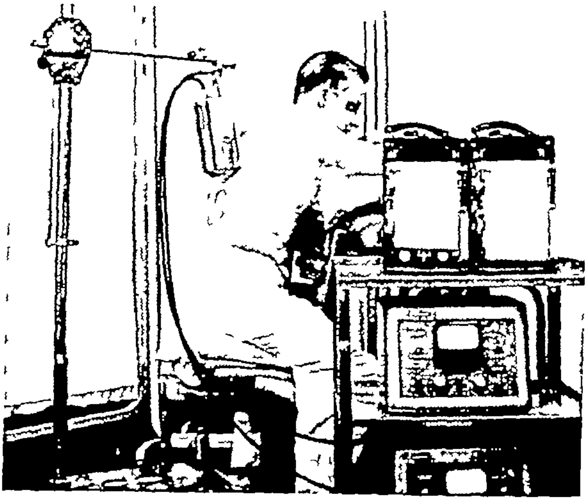


FIG 1 Test equipment consists of two scintillation probes against patient's back, two recorders on cart and two rate meters in cart

METHOD OF TESTING

Kidney positions were located by upright roentgenography The patient was seated comfortably on a chair, leaning forward over a support (fig 1) The scintillation probes were directed downward toward the posterior aspect of each kidney After the test dose was injected intravenously, the two renograms were recorded simultaneously and were completed by 10 to 15 minutes in patients with normal kidney function and by 20 to 30 minutes in individuals having renal dysfunction or upper urinary tract stasis

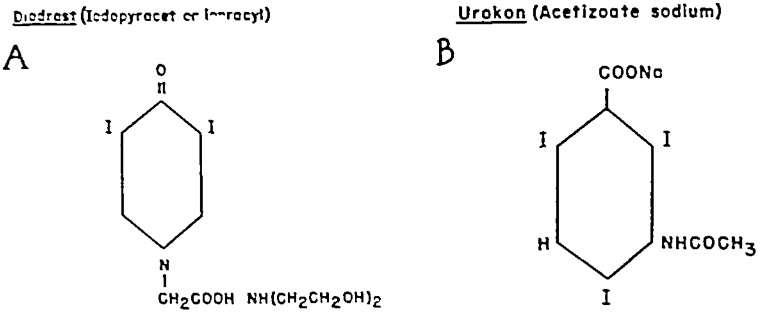
METHOD OF STUDY

Ninety renograms were performed on 33 patients and comparison was made among diodrast, hypaque, miokon and urokon tracings In several patients large doses of nonradioactive contrast media were added to the radioactive tracer dose to determine whether such priming of the kidney would hasten or retard the clearance rate Also, liver uptake and blood clearance tracings were obtained

Urological investigation of these patients included standard blood chemistry, intravenous urography, retrograde pyelography, cystograms for ureteral reflux, standard individual renal function tests and aortography Thirty minute urine samples were collected for radioassay following intravenous injection of tracer doses of the test agents in order to determine their relative rates of urinary excretion

RESULTS

Similar to diodrast and unlike urokon, radioactive hypaque and miokon renograms have characteristic features which reflect active tubular cell secretion and renal excretion rates Figure 2, *A* and *B* are examples of comparative renograms using hypaque, miokon and diodrast A urokon renogram reflecting

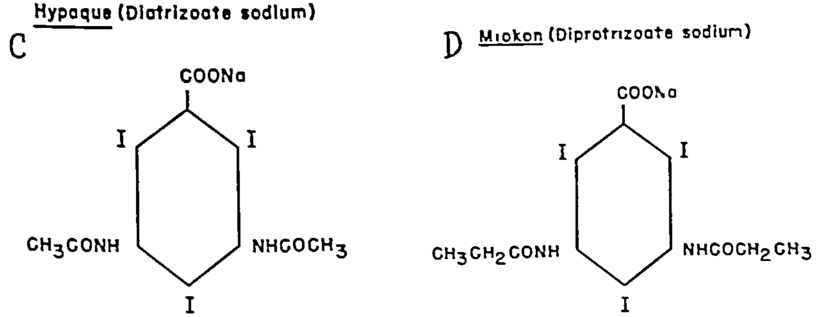


Diodrast (Iodopyracet or [illegible])

Urokon (Acetizoate sodium)

3 5-diiodo-4-pyridone-N-acetic acid diethanolamine

Sodium 2 4,6-triiodoacetylaminobenzoate



Hypaque (Diatrizoate sodium)

Miokon (Diprotrizoate sodium)

Sodium salt of 3 5-diacetamido-2,4,6-triiodobenzoate

Sodium salt of 3 5-dipropionylamino-2,4 6-triiodobenzoic acid

FIG 6

The diodrast-I^{131} hepatogram is similar in form to the rose-bengal-I^{131} hepatogram but the dynamics of diodrast uptake-excretion are several times more rapid than for rose-bengal The thyroid also removes a small amount of diodrast (less than 1 per cent)

In a search through medical literature little information was obtained concerning the mechanisms of renal excretion of hypaque and miokon However from inspection of hypaque and miokon renograms and by comparison with those obtained using diodrast these contrast media are also actively secreted by the renal tubular cells but not quite so rapidly

Urokon which is quite similar in chemical structure to both miokon and hypaque (fig 6) has been subjected to renal clearance studies in the dog by Porporis and associates[5] They found that with low plasma-urokon concentrations tubular cell secretion occurs in sufficient amount to depress PAH clearance However with higher plasma levels (over 30 mg per cent) urokon was cleared

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[5] Porporis A A Elliott G V Fischer G L and Mueller, C C The mechanism of urokon excretion Am J Roentgenol 72 995–1003 1954

TABLE 1 *Radioassay of 30 minute urine samples*

Medium	Normal Kidney	Abnormal Kidney
	%	%
Diodrast I¹³¹	57	25
Hypaque I¹³¹	25	10
Miokon-I¹³¹	17 6	6 8
Urokon I¹³¹	12	

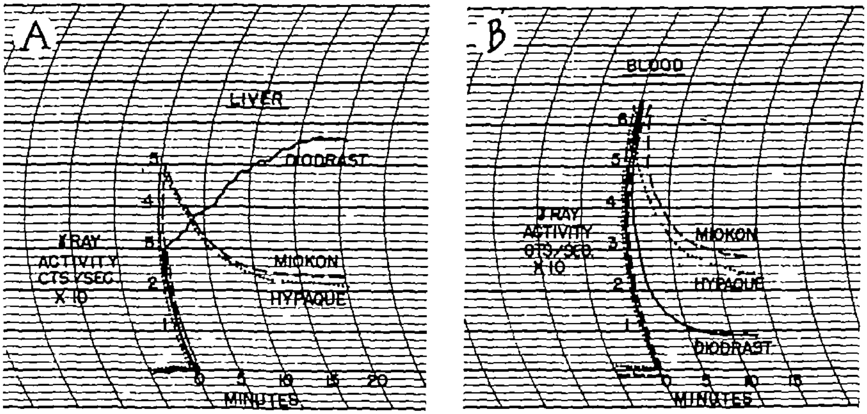

FIG 5 *A*, secondary rise in diodrast hepatogram represents active metabolism by liver In contrast, miokon and hypaque hepatograms do not show liver pickup but merely reflect falling blood levels

B, diodrast blood level falls more rapidly than those of other contrast media

glomerular filtration only is shown in figure 3 The effects of a priming dose are presented in comparative diodrast and urokon renograms in figure 4 The rate of diodrast secretion was decreased while the filtration rate of urokon was increased Priming had little effect on hypaque and miokon tracings

Radioassays of 30 minute urine samples of the test materials are shown in table 1 Values for the excretion of diodrast-I¹³¹ are much higher than those for the other three agents tested

Typical liver uptake and blood clearance tracings are shown in figure 5

DISCUSSION

From the results of this study it is apparent that hypaque-I¹³¹ and miokon-I¹³¹ are extracted from renal blood vessels and excreted into the urinary tract by mechanisms similar to those of diodrast

Smith[4] has shown that diodrast, in low concentrations, is extracted from the blood and actively secreted by the renal tubular cells Its clearance rate is therefore a measure of tubular cell function

Although the kidneys are the chief organs of human diodrast clearance, the liver extracts a limited but significant portion of circulating blood diodrast as shown by simultaneous renograms, hepatograms and blood clearance tracings material is excreted by the kidneys more rapidly than hypaque, miokon or urokon.

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[4] Smith, H The Kidney Structure and Function in Health and Disease New York Oxford University Press, 1951

SUMMARY

Presently, of the four I^{131}-labeled urographic contrast media (diodrast, urokon, hypaque, and miokon) studied by an external test procedure (the radioisotope renogram) for renal function, diodrast-I^{131} is the most satisfactory because of its rapid and active secretion by the renal tubular cells. Miokon-I^{131} and hypaque-I^{131} could be used but the time required for the test would be increased. Urokon is so slowly excreted that it is unsatisfactory for use in a rapid external test for individual renal function.

Diodrast-I^{131} remains as the radioactive contrast medium most worthy of continued clinical investigation in an external radioisotope test for individual kidney function.

chiefly by glomerular filtration Human studies are not available Again, from inspection of urokon renograms, urokon in tracer doses appears to be removed slowly from the blood by glomerular filtration This deduction is supported by its slow rate of urinary excretion

In rabbits, diodrast-I^{131} and urokon-I^{131} renograms are nearly identical However, in humans they *are distinctly different*, because only diodrast is actively secreted by the renal tubular cells This function is necessary to produce a positive uptake segment (b) in the renogram

The human liver does not appear to extract significant amounts of I^{131}-tagged hypaque, miokon or urokon (fig 5, *A*), and their hepatograms reflect only their rates of blood clearance Only a few instances have been reported of visualization of the human biliary system following injection of urographic contrast media [6] The exact amounts and mechanisms of hepatic transport of urographic media remain to be determined

Priming the kidneys with large doses of non-radioactive hypaque, and/or miokon produced no significant difference in the radioisotope renograms when compared with those obtained from unprimed patients Radioassays of 30 minute urine samples also disclosed little differences in rates of renal excretion These findings indicate another difference in the mechanism of renal clearance of the urographic media Large priming doses (8–12 gm) of stable diodrast cause a 5–10 fold reduction in the clearance rate of diodrast-I^{131}, but a similar priming dose of stable urokon causes a definite increase in the clearance rate of urokon-I^{131} (fig 4)

CONCLUSIONS

Distinct differences in renal, hepatic, blood and urine concentration patterns of hypaque, miokon and urokon are found when compared with diodrast Small doses of diodrast are rapidly secreted by the normal renal tubular cells but urinary excretion *is sharply reduced by a priming* dose of stable diodrast The radioactive diodrast renogram provides a means for estimating renal tubular cell function externally, and when performed using the priming procedure it may have additional value in estimating functional renal reserve However, because diodrast is also extracted from the blood by the liver, interpretation of right *renograms may be complicated occasionally*

Hypaque and miokon, which are secreted by renal mechanisms similar to diodrast, but not excreted in part by the liver, appear to have value as tracer materials in the radioactive renogram test However, they are less practical than diodrast for use in a *rapid* screening procedure

Small doses of urokon appear to be slowly filtered by the renal glomeruli and urokon has little clinical value as an individual renal function test using external techniques

The 30 minute urine radioassay values of the four urographic agents corroborate the renogram In spite of hepatic competition for diodrast-I^{131}, this material is excreted by the kidneys more rapidly than hypaque, miokon or urokon

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[6] Arendt, J and Zgoda A The *heterotropic excretion of intravenously injected contrast media* Radiol , 68 238–257, 1957

SUMMARY

Presently, of the four I^{131}-labeled urographic contrast media (diodrast, urokon, hypaque, and miokon) studied by an external test procedure (the radioisotope renogram) for renal function, diodrast-I^{131} is the most satisfactory because of its rapid and active secretion by the renal tubular cells Miokon-I^{131} and hypaque-I^{131} could be used but the time required for the test would be increased Urokon is so slowly excreted that it is unsatisfactory for use in a rapid external test for individual renal function

Diodrast-I^{131} remains as the radioactive contrast medium most worthy of continued clinical investigation in an external radioisotope test for individual kidney function

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DIFFERENTIAL UROFLOMETRY

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The problems of the act of micturition are central to the specialty of urology Obstructive diseases of the lower urinary tract are among the most prevalent problems encountered by the urologist and the correction of such obstructions among the principal surgical aims of our specialty Of less frequency but similar importance are the problems of bladder dysfunction, of neurogenic or myogenic origin

These two disease categories often present with similar manifestations slow, ineffective and hesitant urination, with incomplete emptying and the sequelae of stasis, chronic infection, and upper tract damage In many cases, physical examination and well established testing procedures will serve to indicate the type and degree of the disorder However, this is not always the case Furthermore, many patients, particularly in the older age group, may present themselves with both types of disease

An objective measurement is necessary for critical evaluation of voiding The determination of the residual urine is a well established measurement of this type Other means of evaluating the ability of the patient to void have been proposed but have been found lacking in accuracy, are inconvenient for office use, or are otherwise impractical Recently Kaufman has devised a urine flow meter to measure the actual rate of delivery of urine from the urinary meatus in a quantitative and graphic manner, convenient to use and capable of reproducible results Measuring as it does the actual rate of delivery of urine, in the usual posture of urination, it is a means of evaluating directly the patient's functional impairment

However, in the process of using this device on a series of patients, it was apparent that an impaired rate of delivery might, in a given patient, be due either to obstructive disease or bladder dysfunction, since normal urination requires both a normally functioning bladder and an adequate outlet To dissociate these two factors, it is necessary to hold one constant and evaluate the other This was done in the series reported here by measuring the patient's ability to void through a standard bladder outlet, supplied by inserting a catheter of standard size, and recording the effectiveness of bladder force through such a catheter determined by means of the urine flow rate This represents the patient's potential ability to void in the absence of obstruction By comparing the patient's ability to void in the normal manner, without a catheter, with his ability to void through a catheter of standard size, the effect of the obstructive factor on the urine flow rate can be determined In this way, each factor the bladder outlet and the bladder force, can be investigated

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* Robert S Fox Foundation Student Research Fellow

It is recognized that the force applied to the urine is the sum of detrusor contraction, position, and the abdominal musculature The forcefulness of the stream as it issues from the meatus is this sum less the resistance afforded by the urethra and its constrictive diseases Leaning may also result in an improved flow

METHOD

Patients included in this study were seen with complaints primarily of prostatism, retention, chronic pyuria, and neurologic disorders, demonstrated or suspected The age range was from 17 to 93, most of the patients were elderly men with prostatic obstruction

After voiding, patients were catheterized for residual in the supine position, this value being recorded Through the catheter, 250 or 300 cc sterile saline was instilled, following which the patient voided in the standing position, through the catheter, into the uroflometer A similar amount of saline was reinstilled, the catheter removed and the patient again voided into the uroflometer The discrepancy between the amount instilled and the amount voided without catheter was recorded as the "residual by difference," and, in most cases, correlated very well with the original residual

Following surgery, the entire procedure was repeated with one variation postoperatively, the patients were usually wearing indwelling catheters therefore, there was no initial residual to record Postoperative records were made within the first week following surgery, there appeared to be little or no change in the values subsequently

The operative results reported here are limited to transurethral resections of the prostate

Measurements of urine flow rate were made with the recording uroflometer, which produces a continuous record on which urine output in milliliters is plotted against time in seconds The slope of the resulting curve represents the rate of voiding in milliliters per second and can be directly read from the tracing The

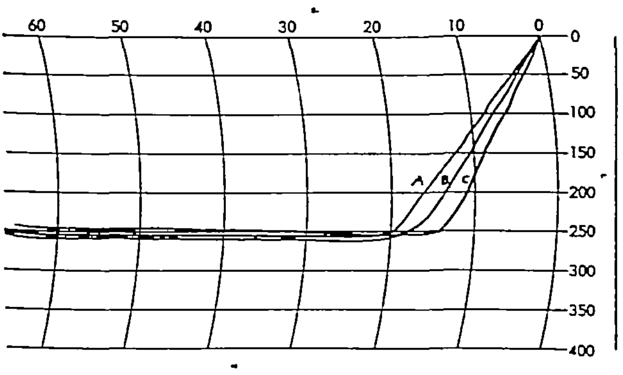


FIG 1 Rate of delivery of saline under 50 cm hydrostatic pressure through standard Foley retention catheters all with 30 ml bag inflated Tracing A 18F 13 ml per second B 22F 15 ml per second C 26F 18 ml per second

values reported here are rates read from the steepest straight line portion of the tracing of reasonable duration and are recorded to the nearest whole milliliter per second Since the total quantity voided is readily read from the tracing, the residual by difference is readily computed

Catheters used in this series were principally size 20F straight red rubber catheters, and Foley type catheters, 18, 20, and 22F To calibrate these, flow rate determinations were done by permitting saline to flow through the catheters under 50 cm of saline hydrostatic pressure The average rate of flow through a random sampling of size 20 straight red rubber catheters was 20 ml per second This is equal to the low normal rate reported by Kaufman and confirmed by us The rates of flow through size 18, 22, and 26 Foley catheters, with 30 cc bags is shown in figure 1 as tracings *A*, *B*, and *C*, respectively, and are equal to 13, 15, and 18 ml per second There was no significant difference between the rates with the retention bag inflated and deflated

OBSERVATIONS AND DISCUSSION

An example of the most frequently seen disease entity in the group of patients reported is shown in figure 2 Patient E R , a 67-year-old man with one episode of acute retention due to benign prostatic hypertrophy, had a residual of 75 ml and could produce only 1 ml of urine per second (tracing *A*) unassisted Through a size 20 straight rubber catheter he delivered 11 ml per second, with a residual

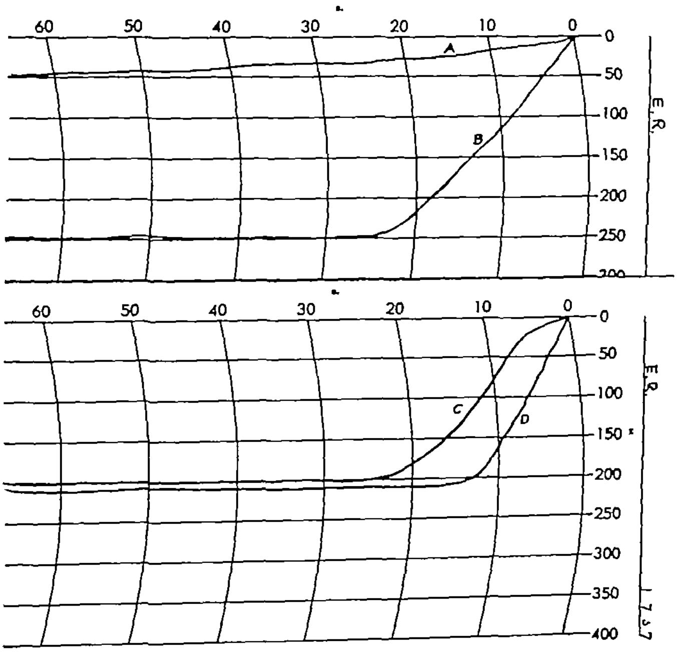


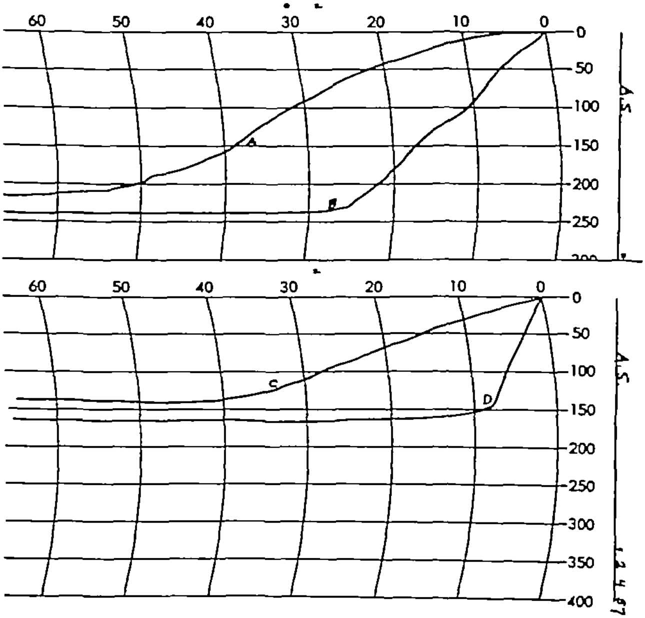
Fig 2 A Preoperative tracing without catheter B Preoperative tracing with 20F straight rubber catheter C Postoperative tracing without catheter D Postoperative tracing with 20F straight rubber catheter

by difference of 200 ml Postoperatively, he had no residual, a flow rate without catheter of 16 ml per second (*C*) and 16 ml per second with a catheter of the same size and type (*D*) The residual difference was zero

A comparison of tracings *B* and *D* demonstrates that there is an improvement in the bladder force as measured by the flow through the standard catheter at two different times This is frequently seen when patients are placed on continuous drainage, as this man was, following a period of chronic obstruction The same finding occurs following surgical relief of obstruction

This occurrence is seen more clearly in figure 3, which consists of two sets of tracings made by A S, an 86-year-old man with benign prostatic hypertrophy, who was placed on continuous drainage for a prolonged period Tracings *A* and *C* are the urine flow rates without catheter and are 6 and 4 ml per second, respectively Tracings *B* and *D*, the rates through a size 20 Foley catheter, show an improvement from 9 ml per second to 20 ml per second This represents an improvement of the expulsive force of the bladder and a restoration to normal after a period of chronic obstruction with detrusor atony

Not all patients placed on drainage show this return of bladder function, and this failure to improve is important N W, a 62-year-old man with benign prostatic hypertrophy, had, initially, a flow rate of 4 ml per second (fig 4, *A*) without catheter and 9 ml per second (*B*) with catheter One month later (*C*, *D*), after retention catheter drainage, the rates had not improved No neurologic



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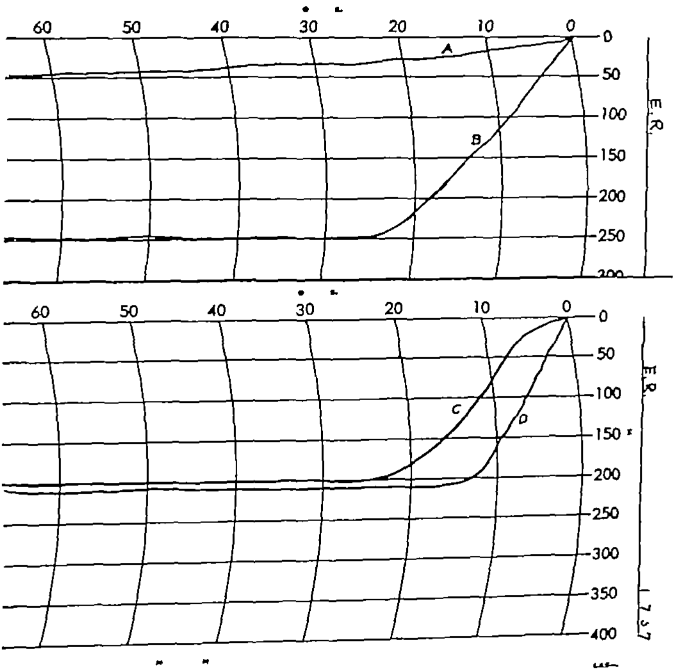

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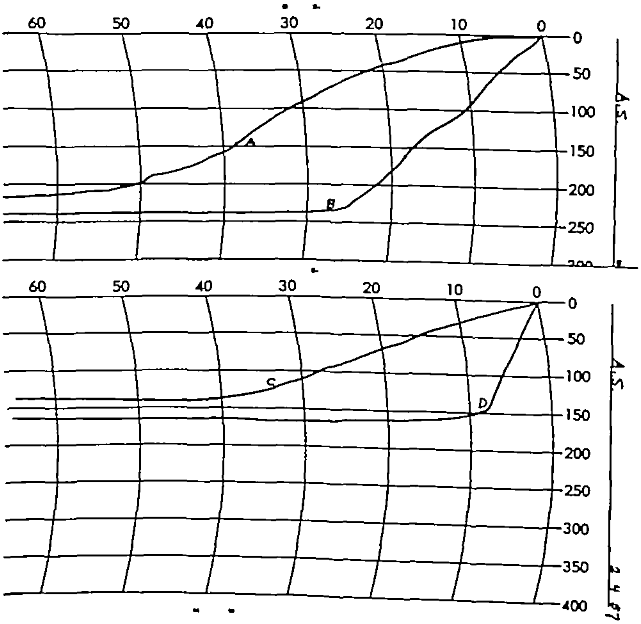

FIG 3 A Tracing without catheter B Tracing with size 20 Foley catheter C Tracing without catheter following period of drainage D Tracing with size 20 Foley catheter following period of drainage

basis for bladder dysfunction could be demonstrated, but on the basis of this poor potential capacity to void, a limited success from prostatic resection was predicted for this patient Following transurethral resection, his rates are shown by *E* and *F* of figure 4, tracings which show that with and without the catheter he delivered 10 ml of urine per second, i e , that the urethra was capable of removing the urine as rapidly as the bladder could expel it The residual by difference was 40 ml Postoperatively, acute retention developed, satisfactorily treated by 24 hours of catheter drainage *Cystoscopically, no bladder neck* obstruction was present

Another and more obvious cause of poor flow rate postoperatively is inadequate resection of the obstruction Figure 5 demonstrates tracings made of the urine flow rates of R L , 84-year-old man with benign prostatic hypertrophy and one episode of acute retention Tracings *A* and *B* represent his function preoperatively and *C* and *D* the postoperative tracings While the residual by difference and

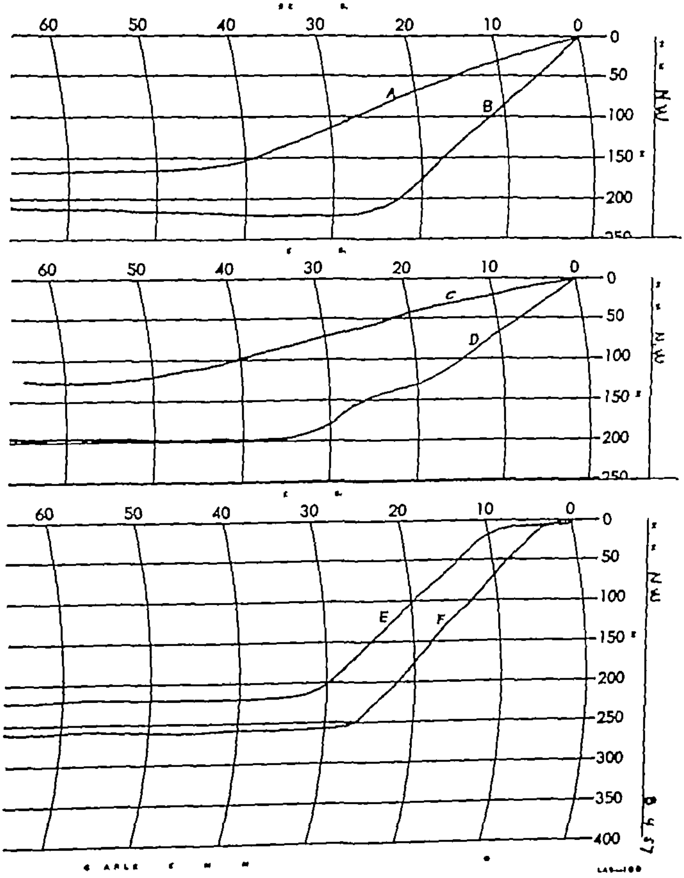

Fig 4 A and B Tracings without catheter and with catheter, preoperatively C and D Tracings without catheter and with catheter, preoperatively, but following period of continuous drainage E and F Tracings without catheter and with catheter, postoperatively

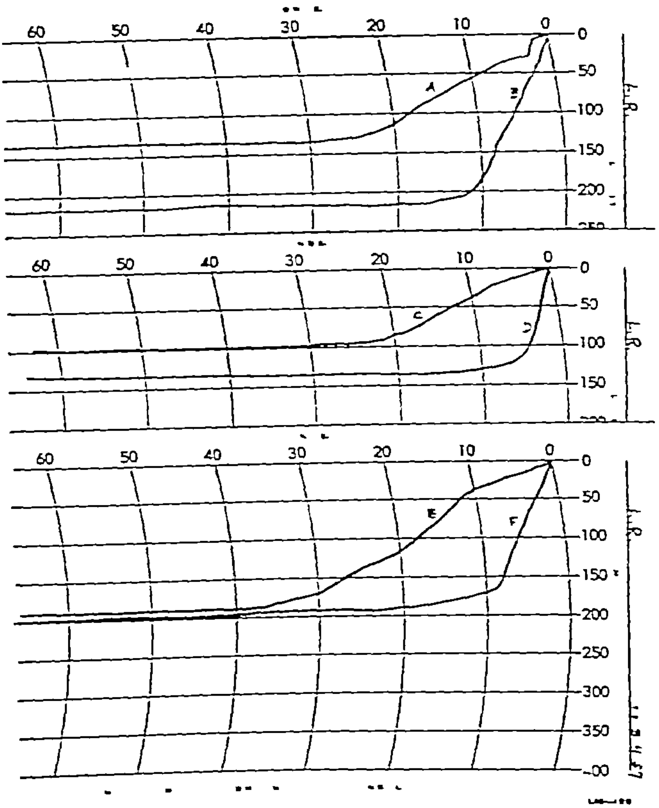

FIG 5 A and B Preoperative tracings without and with catheter C and D Postoperative tracings without and with catheter following first transurethral resection E and F Postoperative tracings without and with catheter following second transurethral resection

the rate with the catheter (reflecting drainage effect) were improved, the rate without the catheter was essentially unchanged A second transurethral resection was done, after which the residual, and residual by difference, were both near zero but still the unassisted flow rate was poor This was determined to be due to a urethral stricture, which, when dilated allowed a satisfactory flow

The comparison of the unassisted flow rate to the potential rate of flow, as measured by the flow through the catheter, has, at times been of assistance in determining probable value of surgery to a given patient H.K., a 93-year-old man in relatively good health demonstrates this point by the tracings shown in figure 6 in which *A* represents the rate without catheter, and *B*, the rate with size 18 Foley catheter following several weeks of drainage His uropathy was carcinoma of the prostate apparently arrested by orchiectomy and stilbestrol therapy His complaints were those of chronic pyuria, secondary to a residual of 3–400 ml moderate azotemia (blood urea nitrogen 65 mg per cent) and a minor, but troublesome incontinence Cystoscopy revealed mild to moderate

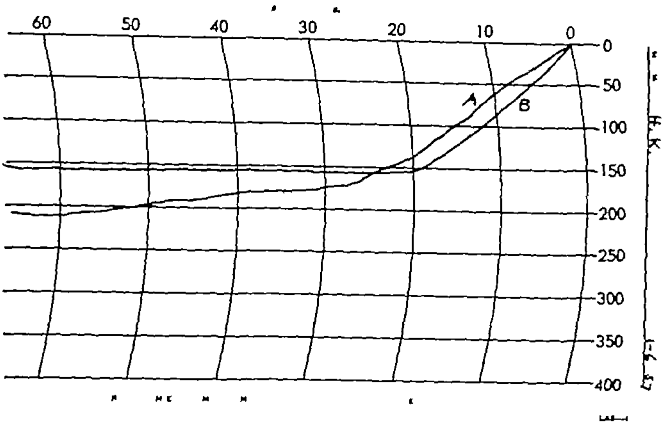

FIG 6 A Tracing without catheter B Tracing with size 18 Foley catheter following period of continuous drainage

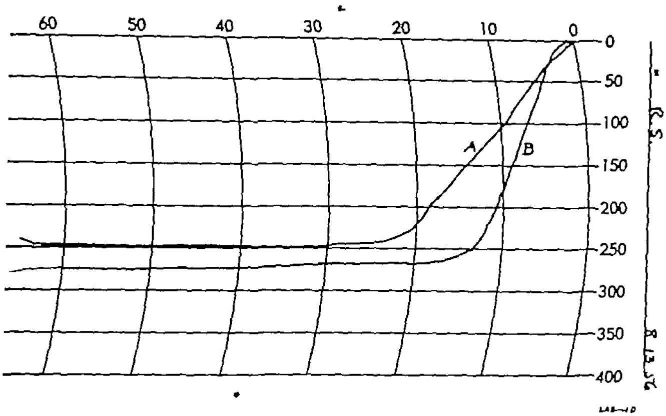

FIG 7 A Tracing with size 18 Foley catheter B Tracing without catheter

bladder neck obstruction, and the tracings show that the bladder emptied as rapidly without the catheter (7 ml per second) as with it (8 ml per second), indicating that the impairment of function was at the level of bladder function and not significantly obstructive He was placed on permanent drainage, with reduction of his blood urea nitrogen, improvement of his infection, and avoided surgery, which did not promise him much improvement

Figure 7 demonstrates the tracings made by R S, a 17-year-old boy who had Hirschsprung's disease which had been resected, and hydroureters He was evaluated by means of catheter flow studies to determine if any obstructive or neurologic disorder of the bladder might be contributing to his hydroureters His initial residual was less than 10 ml His cystogram and cystoscopic examinations of the bladder neck showed no abnormalities His flow rate with a size 18F Foley catheter was 11 ml per second, and without the catheter, 20 ml per second Thus, in his instance, the catheter represented an obstruction, compared to the bladder neck This is the situation in normal circumstances

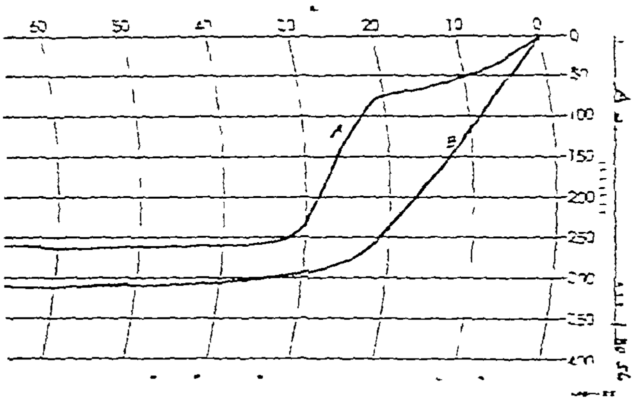

FIG 8 A Tracing without catheter B Tracing with size 20 Foley catheter

In this case it indicated the absence of either obstructive disease or deficient bladder force.

Another and different use of the urine flow rate tracing is demonstrated in figure 8 which shows the tracings of urine flow rate without catheter (*A*) and with size 20 Foley catheter (*B*) in a 25-year-old woman with two episodes of alleged inability to void. Seven hundred and 1000 ml of urine were drained from the urinary bladder on these occasions. Cystoscopy showed no abnormalities, spina bifida occulta was noted, and the cystometrogram was flat, the pressure reaching but 15 ml of water after 700 ml were instilled. She was felt to be psychoneurotic and was taking equanil 400 mg q.i.d. She had been under long term urological management for cystinuria. Stopping the equanil did not affect the cystometrogram or her feeling of inability to void. Finally, the urine flow rate tracings shown in figure 8 were made which demonstrated (tracing *A*) that after a rather poor beginning she could void at a rate of 18–20 ml. per second, actually better than her rate with the catheter. With this information for support she was convinced that her voiding ability was adequate and with encouragement and psychotherapy overcame the feeling of inability to void. She now is doing well and carries no appreciable residual.

CONCLUSION

The tracings described above are representative examples of those which have been seen in the course of observations of urine flow rates with and without catheters in a series of urological patients. They appear to demonstrate several features.

The flow rate through the catheter eliminates the obstructive variable of the patient's disease and provides an indication of the potential rate of which the patient would be capable if the existing obstruction were removed. On this basis it is possible to predict with some assurance which patients would benefit from resection of the obstruction and which would achieve limited improvement. While some have an unassisted (without catheter) rate postoperatively which is better than the preoperative rate with the catheter, this is distinctly uncomm in this series

When the postoperative urine flow rate is not as much improved as anticipa even though the residual may be improved, this is good evidence that the re tion may have been inadequate or that some other factor is intervening, e stricture The postoperative flow rate is a valid and superior method of chec the adequacy of resection with no more instrumentation than for determinatio of residual urine In practice, postoperative flow rates can be checked witho catheterization if the patient fills the bladder by natural means

Continuous catheter drainage of the urinary bladder can be demonstrated t improve the potential function of the bladder, as indicated by the rate wi catheter, in the case of chronic urinary tract obstruction Such improvemen should not be overlooked in predicting the probable benefit to the patient o removal of obstruction

In this series, this graphic method of demonstrating the nature of the obstruction and the relatively poor urine flow without a catheter was of much benefit in explaining to patients with obstructive uropathy the degree of ob*obstruction and the desirability of correction*

SUMMARY

A method is presented to evaluate separately the effects of obstructive uropathy and poor bladder function in cases of incomplete or slow urination, by means of measurements of urine flow rates Representative examples are presented and discussed

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CYTOLOGICAL STUDIES OF THE URINE: PRELIMINARY REPORT

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PURVIS L. MARTIN AND THOMAS A. SLATE

Diagnostic methods in urology are quite reliable and yet some clinical problems demand additional information. Cytologic studies of the urinary sediment by others have indicated that the method is clinically unreliable. Recently Roland and Marshall reported more optimistically, as did Harrison in 1951.

Martin and Slate, working in the gynecology-obstetrics cytological laboratory, have made over 60,000 cervical cytological studies in San Diego. Their cytologic experience and facilities were made available for this experimental study.

SUBJECTS

During the past 18 months the urines of 121 male and 97 female patients (218 total) were examined. Of these, 61 (28 per cent) had proven malignant lesions of the urinary system. Some were selected for the study, but the majority were chosen at random from private patients.

METHODS

The urine of all female patients was obtained by catheterization and from the males by voiding or instrumentation. A minimum of 50 cc urine was slowly centrifuged. The sediment was smeared and fixed in alcohol and ether and stained by a modified Papanicolaou method. Staining and screening of the slides were performed by trained cyto-technicians. All atypical, suspicious, or positive smears were reviewed by one of the authors (Slate). Clinical information was not available to the cytologists.

The classification of smears was similar to that utilized in cervical smears. The earliest detectable anaplastic cell with malignant characteristics placed that smear in the suspicious or positive groups. The classes were:

Class 0. Insufficient cellular elements on the smear to permit classification.

Class 1. Negative for malignant cells.

Class 2. Atypical cells present (not suspicious of cancer). The type of abnormal cell was specified. The cytologist usually suspected a benign or inflammatory change.

Class 3. Highly atypical cells present. The type of abnormal cell was specified. A marked atypical lesion or premalignant lesion was suspected.

Class 4. Highly suspicious of malignancy.

Class 5. Positive for malignant cells.

RESULTS

A report of class 4 or 5 smear has to this date indicated that the patient harbored a genitourinary cancer. Of the 61 patients with known malignant neoplasm involving the urinary system 21 yielded class 4 or 5 smears. The sources of the exfoliated cancer cells in the urine are listed in table 1.

Neoplasms originating from transitional cell epithelium were more easily de-

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Read at annual meeting of Western Section of American Urological Association, Seattle, Wash., May 27-30, 1957.

TABLE 1 *Sources of exfoliated cancer cells in the urine*

	No of Patients	Class 4	Class 5
Bladder carcinoma (grade 1–4)	34	5	9
Carcinoma of renal pelvis	3	1	1
Carcinoma of renal parenchyma	3	1	0
Carcinoma of prostate	20	3	0
Carcinoma of urethra	1	1	0
Totals	*61*	*11*	*10*

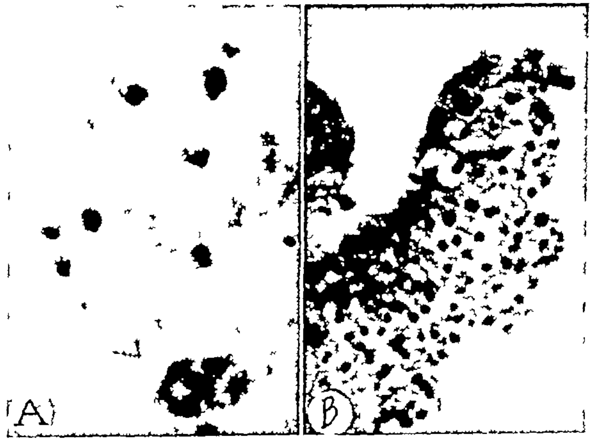

FIG 1 Case 1 *A*, class 4 Papanicolaou smear of urine shows numerous malignant cells with relatively large and darkly staining nuclei (× 20) *B*, photomicrograph of bladder biopsy shows transitional cell carcinoma (× 20)

tected by cytological study In addition to fourteen class 4 and 5 smears from 34 bladder tumors, there were seven class 3 smears

In the 157 patients without malignant neoplasm of the urinary system, 86 (48 per cent) produced class 0 (unsatisfactory) smears, 46 (29 per cent) class 1, 22 (14 per cent) class 2, and three (2 per cent) class 3

ILLUSTRATIVE CASES

The following case histories are presented as examples of urinary cytology assisting in the diagnosis and management

Case 1 C F B was aged 75 years A grade 3 transitional cell vesical carcinoma was resected transurethrally in January 1955 Twice in the next year cystoscopy revealed no recurrence A class 4 Papanicolaou smear was reported (fig 1, *A*) in March 1956 Cystoscopy then revealed an area of red, irregular mucosa on the right posterosuperior wall of the bladder This area was not typical of malignancy However, biopsy demonstrated transitional cell carcinoma (fig 1, *B*) The Papanicolaou smears were class 4 and 5, five and six months later Biopsy was obtained from another "suspicious" area, then fulguration applied The tissue again revealed transitional cell carcinoma, grade 2 Since then, repeated smears of the

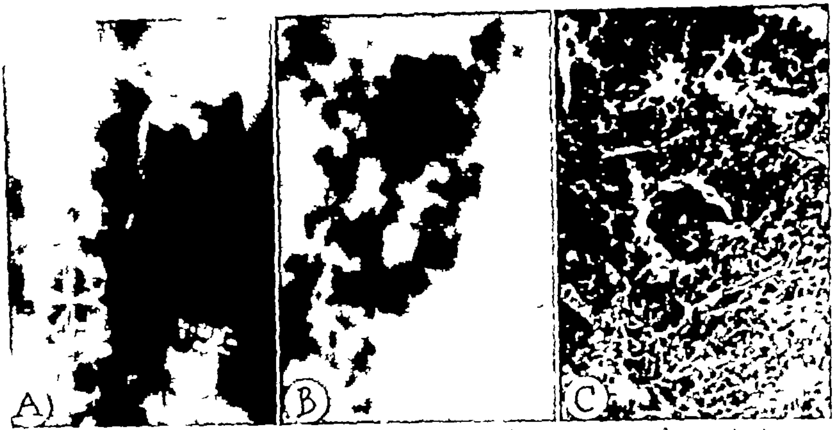

Fig 2 Case 2 *A*, retrograde left pyelogram through ureterotomy demonstrates irregularity of pelvis and calyces *B*, Papanicolaou smear, class 5, of urine from left renal pelvis shows numerous malignant cells with large and dark nuclei (× 45) *C*, photomicrograph of tumor from left renal pelvis demonstrates irregular folds of undifferentiated transitional epithelium (× 10)

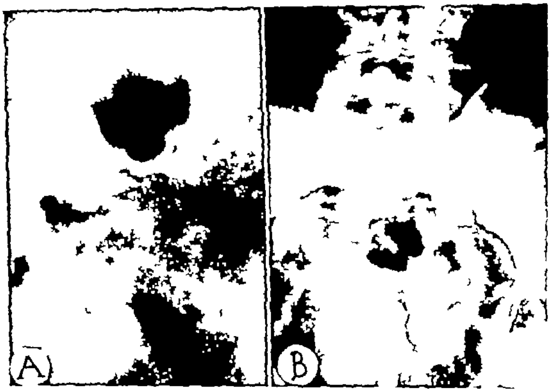

Fig 3 Case 3 *A*, Papanicolaou smear, class 5, of urine obtained from bladder shows large malignant cells (× 45) *B*, left bulb ureterogram shows irregularity and obstruction in lower ureter probably from neoplasm

urine have not disclosed malignant cells and recent cystoscopy gave no evidence of neoplasm

Comment The Papanicolaou smears repeatedly called attention to the existence of a malignant lesion in the bladder that was verified by biopsy

Case 2 P C was aged 43 years Total cystectomy and *ureterosigmoidostomy* were performed for invasive transitional cell carcinoma of the bladder in January 1953 The patient did well until two years later when left renal pain and rectal hematuria developed The excretory urogram failed to demonstrate function of the left kidney, causing suspicion of obstruction at the left ureterosigmoidal anastomosis Surgical exploration revealed a patent anastomosis but retrograde pyelography (fig 2, A) through a ureterotomy indicated either cicatricial pyelonephritis or carcinoma of the left renal pelvis Urinary smears from the left renal pelvis demonstrated malignant cells (fig 2, *B*) Nephro-ureterectomy was performed with removal of a transitional cell carcinoma of the renal pelvis (fig 2, *C*) The patient expired from extensive metastases five months later

Comment The smears of urinary sediment from the left kidney aided in the diagnosis of this complicated problem

Case 3 M M, aged 63 years, underwent transurethral resection of a transitional cell carcinoma from the left posterior bladder wall in January 1956 Urography at that time demonstrated normal kidneys and ureters Three cystoscopic examinations during the following year revealed no recurrence of vesical neoplasm A Papanicolaou stain of the urinary sediment (fig 3, *A*) was then reported class 5 This prompted restudy with bulb ureterograms (fig 3, *B*) which demonstrated a probable neoplasm in the pelvic segment of the left ureter Surgical exploration is to be performed

Comment *A class 5 cytologic report resulted in a repeat study of this patient* with detection of a probable new focus of carcinoma

Case 4 R K, aged 56 years, was admitted to the hospital because of vaginal bleeding from uterine fibroids, and hematuria Retrograde pyelography demonstrated a filling defect (fig 4, *A*) in the right kidney suggestive of a neoplasm Smears of the urine from the bladder and right kidney were reported class 4 (fig 4, *B*) At surgical exploration, the exterior of the right kidney appeared normal, but because of the previous findings, nephrectomy was performed Pathological examination demonstrated papillary transitional cell carcinoma of renal pelvis, grade 2 (fig 4, C) Hysterectomy and ureterectomy were done eight days after the nephrectomy

Comment The Papanicolaou smear gave support to the diagnosis of neoplasm of the right kidney The patient is to be followed with periodic urologic studies, including urinary cytologic examination

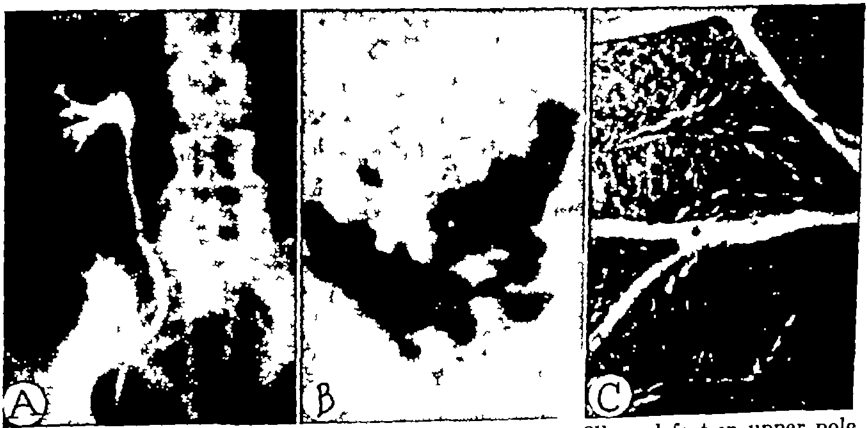

FIG 4 Case 4 *A*, retrograde pyelogram demonstrates filling defect in upper pole of right kidney *B*, Papanicolaou smear, class 4, of urine obtained from right kidney shows clusters of malignant cells (X 45) *C*, photomicrograph (X 10) shows papillary folds of transitional cell carcinoma of right renal pelvis

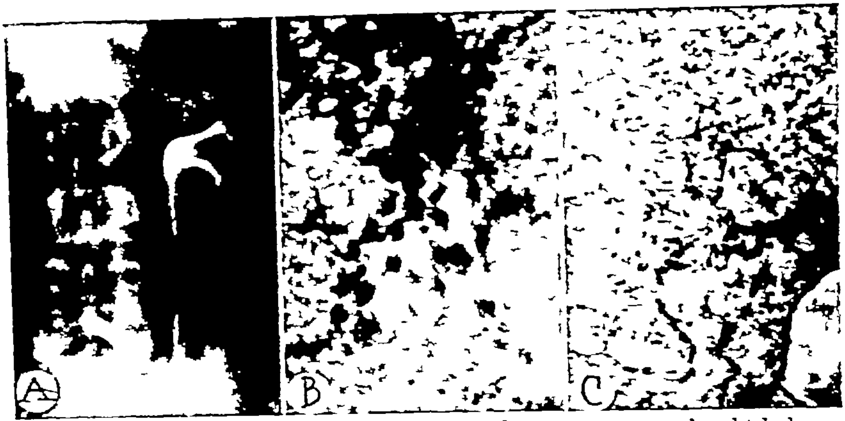

FIG 5 Case 5 *A* retrograde pyeloureterograms demonstrate normal right kidney and tumor in upper pole of left kidney *B* Papanicolaou smear class 4 of urine from bladder shows numerous malignant cells among red blood cells (× 20) *C* photomicrograph of left renal neoplasm shows clear cell carcinoma (hypernephroma) (× 20)

Case 5 L C aged 59 years had been losing strength and weight for 3 months Gross bleeding from the right ureteral orifice was seen at cystoscopy The right pyeloureterogram was normal (side of bleeding) but a large tumor was seen in the upper pole of the left kidney (fig 5 *A*) Class 4 cells (fig 5, *B*) were reported in the bladder urine and class 3 in urine from each kidney At surgical exploration a large hypernephroma necessitated left nephrectomy (fig 5, *C*) The patient has remained well except for failure to regain normal weight Urinary cytology five months after operation was class 1

Comment The initial report of a class 4 smear gave credence to the suspicion of urinary cancer in this patient It was difficult to decide to remove the left kidney when the right was bleeding The identification of malignant cells in the urine aided in the decision. The patient is being followed with periodic urologic studies including cytologic smears

DISCUSSION

It is encouraging that no false-positives have been reported Confusion of urine specimens at collection resulted in one temporary false-positive until the error was clarified This emphasized that the method is a laboratory aid and does not make positive diagnoses To operate upon a patient solely on the basis of a positive smear would be folly and give the method further disrepute Our experience indicates that it is only a supplement to recognized urological diagnostic methods The present method alone is valueless as a screening method since the absence of malignant cells in the urine does not exclude urinary cancer

Forty of our patients with known urinary malignancy did not yield smears positive for cancer cells Twenty-three of the 40 smears were classed as 0 (unsatisfactory) This emphasizes the need to obtain more cells for examination on the individual slide We plan to smear the sediment from a larger volume of urine and a method of filtering cellular elements from larger volumes of urine is to be considered However, false-negative reports cannot be totally eliminated since a neoplasm may intermittently exfoliate malignant cells into the urine

Our studies suggest that cytologic examination of the urine is of greatest value in the diagnosis and progress examinations of patients with transitional cell carcinoma Since these tumors are sometimes multicentric in origin, cytologic studies may lend support to, or demand, cystoscopic and pyelographic study It is to be expected that early peripheral tumors in the renal parenchyma and prostate gland would be most difficult to detect by urinary cytologic smears The three class 4 smears from patients with prostatic carcinoma had far-advanced and large neoplasms

The method of staining is complicated and accurate interpretation requires much cytological experience It is apparent that greater experience with urinary cytology by personnel trained in cytology is needed One may predict that urinary cytology would be more frequently helpful to the clinician if sufficient representative cells could be placed under the microscope of the cytologist

SUMMARY

Cytologic studies of the urinary sediment from 218 urological patients were made

Sixty-one of the patients had known cancer of the genitourinary organs and 21 of these yielded smears positive for malignant cells

Preliminary studies indicated that the method may have its greatest value in the progress examinations of patients with transitional cell carcinoma

No false-positives were reported

Improved methods to place more urinary epithelium on slides submitted for study are needed to avoid frequent false-negatives and class 0 reports

Acknowledgments are given to James E Sandell, M D , for the photography, and to John W Merritt, B S , chief technician at gynecology-obstetrics laboratory, for supervision of the staining and screening of the smears

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CALCIUM PHOSPHATE SOLUBILITY IN URINE AS MEASURED BY A PRECIPITATION TEST EXPERIMENTAL UROLITHIASIS XIII

C W VERMEULEN, E S LYON AND G H MILLER

From the Department of Surgery, University of Chicago, Chicago 37, Ill

An attempt is made in this paper to explain the supersolubility of calcium phosphate in urine, in the succeeding paper a similar attempt will be made for calcium oxalate By supersolubility we mean that the concentrations of phosphate, oxalate, and calcium are much higher in urine than in completely saturated water solutions of either calcium phosphate or calcium oxalate Of course the acidity of urine increases solubility, especially in the case of calcium phosphate, but even at an equivalent pH, urine exhibits supersolubility with respect to water A variety of explanations have been offered to account for this apparent violation of the solubility product principle A review of the literature will not be attempted, but it may be of value to categorize the various mechanisms that have been suggested 1) salt effect, 2) protective colloids, 3) ion-binding, complexing, and chelation, 4) hydrotropy, 5) true supersaturation and the factor of time

Salt effect The solubility of poorly soluble salts is sometimes increased by the presence of other ions which act in a nonspecific way to change the ionic activity of the components of the insoluble salt The increase in solubility is dependent on the concentration and the valence of the nonspecific ions This type of solubilization may be looked upon as a kind of "salting-in" effect Holt, La Mer, and Chown[1] and Sendroy and Hastings[2] have made valuable experimental and theoretical contributions in this field with regard to calcium phosphate solubility in water Elliot[3] applied "ion activity" calculations to results obtained from a comprehensive analysis of the electrolytes in a series of urines He found that the calcium phosphate ion products were such as to conclude that normal urine was usually unsaturated

Protective colloids It is known that precipitation reactions are sometimes impeded by the presence of certain colloidal materials Since urine contains a small amount of substances having colloidal size, some workers have explained urinary supersolubility by a protective colloid mechanism The protective colloid hypothesis has enjoyed the widest popularity, but its significance has never been

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Ion-binding, complexing, and chelation The solubility of any salt will be increased if one of its component ions becomes bound to some other substance present in the solution One form of calcium binding is classically illustrated by the poorly ionized (Ca Cit) complex ion formed in the presence of citrate Calcium may also be sequestered by certain organic chelating agents with which the calcium enters into a ring structure by means of coordinate bonds Since the calcium actually becomes a part of the ring, it loses its properties as a free ion just as it did with citrate Both Flocks[5] and Vermeulen, Miller and Chapman[9] have presented evidence for some degree of calcium binding in urine

Hydrotropy This term was coined by Neuberg to indicate the solubilizing effect of certain organic salts According to Neuberg,[10] a large number of organic salts have this property, but in most instances these hydrotropic substances must be in high concentration to have any appreciable effect The exact mechanism of action is not understood, though chelation has been suggested As related to urolithiasis, the chief interest in hydrotropic action stems from the work of Prien and Walker[11] who recommend therapy with salicylates to increase excretion of glucuronides in the urine The glucuronide, in turn, is thought to solubilize by hydrotropic action Vermeulen, Finlayson, and Chapman[12] found that significant solubilizing requires a much higher concentration of glucuronide than can be attained with salicylate administration

Supersaturation and the factor of time If a precipitation reaction is an extremely

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Supersaturation and the factor of time If a precipitation reaction is an extremely slow one, a condition of temporary supersaturation exists up until the time equilibrium is attained Precipitation of $Ca_3(PO_4)_2$ is a "fifth order" chemical reaction and therefore proceeds at a slow pace Holt, La Mer and Chown[1] suggested that this may be a partial explanation for the supersolubility of calcium phosphate in the blood Perhaps it ought also to be considered in connection with the supersolubility in urine It may be mentioned that certain dyes are believed to retard precipitation reactions, but Seigle[13] concluded that the chief action of dyes is not a true retardation in precipitation but rather an alteration in precipitation forms and the adhesiveness of the resulting crystals

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METHOD FOR TESTING CALCIUM PHOSPHATE SOLUBILITY

The fluid to be examined for solubility is pipetted into a series of 5 glass-stoppered centrifuge tubes using 10 ml samples To each tube 1 ml of $1/10$ molar calcium chloride is added After mixing, 1 ml of $1/10$ molar di-sodium hydrogen phosphate is pipetted in with constant agitation Calcium phosphate immediately begins to precipitate The tubes are then shaken on a mechanical shaker, one tube for 15 minutes, and one each for 1, 2, 4, and 24 hours (The different time intervals are used to permit observations on the time required for completion of the precipitation reaction) When removed from the shaker, each tube is centrifuged for five minutes to facilitate filtration and then filtered through paper The filtrate pH (glass electrode pH meter) and calcium concentration are now determined Under these conditions the calcium in the filtrate is a measure of the calcium phosphate solubility Comparisons in different fluids are valid if the fluids being compared were originally identical in concentration of calcium and phosphate and were also identical as to pH

Earlier in this work calcium was determined by the standard method in which calcium is precipitated as the oxalate and the oxalate titrated with permanganate More recently we have employed a modified flame photometer technique (Coleman) in which the calcium is first precipitated with ammonium oxalate to eliminate interfering substances, particularly sodium The calcium oxalate is then dissolved in acid and the calcium determined by standard flame techniques Control studies convinced us that the modified flame photometer method is sufficiently accurate and considerably less tedious than the conventional permanganate titration

SOLUBILITY IN WATER SOLUTIONS OF URINARY CONSTITUENTS

Four different water solutions were prepared containing urinary components in concentrations approximating high normal levels The first solution was the most complex, consisting of urea 0 5M, sodium chloride 0 2M, sodium sulfate 0 05M, magnesium sulfate 0 01M, and sodium citrate 0 005M The second solution was like the first except that it contained no citrate Both citrate and magnesium were omitted from the third, while sodium sulfate was also omitted from the fourth solution so that only urea and sodium chloride remained The four

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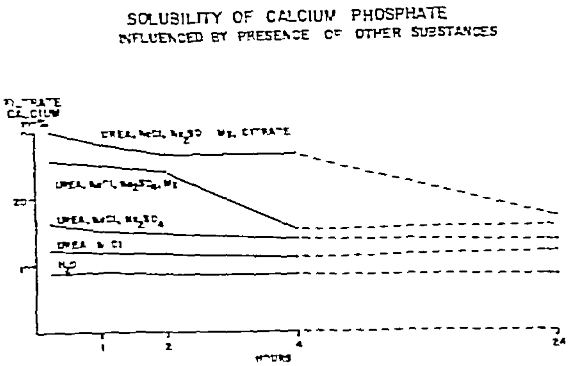

FIG 1 Average results of four experiments using water and progressively more complex solutions all with initial pH of 6 5 ± 0 08 Filtrate calcium is index of solubility and results plotted against time Increase in solubility was cumulative with urea NaCl Na_2SO_4 Mg and Cit In early hours of test Mg and Cit act in special way by permitting temporary supersaturation

fluids were now equalized at pH 6 5 using HCl or NaOH as needed and their solubility for calcium phosphate determined with the test already described A control was simultaneously run using distilled water

The results are illustrated in figure 1 The solubility in the fluid containing only urea and sodium chloride was somewhat greater than in distilled water (Tests with urea alone exhibited little or no solubilizing action) When sodium sulfate was also present the solubility was increased With the fluids containing magnesium or magnesium plus citrate a further striking increase occurred particularly during the early hours of the test, but as time elapsed both magnesium and citrate lost their solubilizing power to a large extent Apparently these substances permit the existence of a state of temporary supersaturation Sodium chloride and sulfate on the other hand increase solubility to a lesser degree but the increase is not dependent on the factor of time This entire experiment was repeated three times always with the same results

To further study the peculiar magnesium and citrate effect solutions were made up containing urea sodium chloride and sodium sulfate in the concentrations used previously but with varying concentrations of magnesium or citrate Figure 2 *A* shows that the effect of magnesium is dependent upon the concentration—the greater the concentration the longer the period of supersaturation A similar result was obtained with citrate (fig 2 *B*) though here the period of supersaturation was of longer duration

We are unable to explain the solubilizing found in the presence of magnesium and citrate but the other type as seen with sodium chloride and sulfate, is doubtless due to the nonspecific salt effect Other experiments have shown the same salt effect with nitrate carbonate ammonium and potassium ions The action is dependent upon the concentration and the valence of the particular ion therein agreeing quite nicely with theoretical physical chemistry Creatinine uric and hippuric acids were also studied but were without significant solubilizing action providing pH was controlled

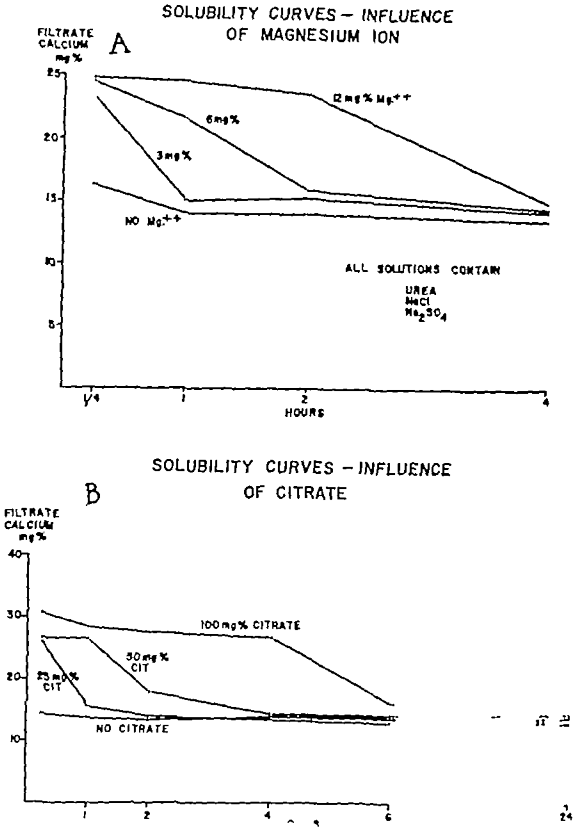

Fig 2 *A*, calcium phosphate solubility curves with four different solutions, all containing identical amounts of urea, NaCl, and Na_2SO_4, but with different amounts of magnesium Initial pH of all solutions was 6 43 ± 0 03 Duration of supersaturation was dependent upon concentration of Mg present Ultimate solubility (4 hours) was same

For typical example of pH change during test, *compare bottom curve vs top Mg curve* initial pH 6 46 vs 6 44, 15 min filtrate pH 6 57 vs 7 13, and 4 hr filtrate pH 6 31 vs 6 37

B, solubility curves with four different solutions, all *containing identical amounts* of urea, NaCl, and Na_2SO_4, but with different amounts of citrate Initial pH of all solutions was 6 75 ± 0 1 Citrate action is similar to action of magnesium seen in *A*

SOLUBILITY IN URINE VERSUS "ARTIFICIAL URINE"

Methods All observations were made using morning urine specimens from normal individuals, and only those containing no visible sediment When the test for solubility was done, some specimens failed to produce an immediate precipitate with the standard amounts of the precipitating agents With larger amounts precipitation did occur but these results have been omitted from this report In doing the solubility tests, determinations of the filtrate calcium levels were made at 15 minutes, 1, 2, 4, and 24 hours after starting the test by the addition of the calcium and phosphate solutions In a few instances additional observations were made at other time intervals as well

The original urine specimens were *analyzed for sodium*, potassium, calcium, magnesium, chloride, phosphate, sulfate, urea, and citrate—all by conventional methods The pH of the original specimen was also determined accurately with the pH meter An *artificial urine was then made up* in distilled water using vari-

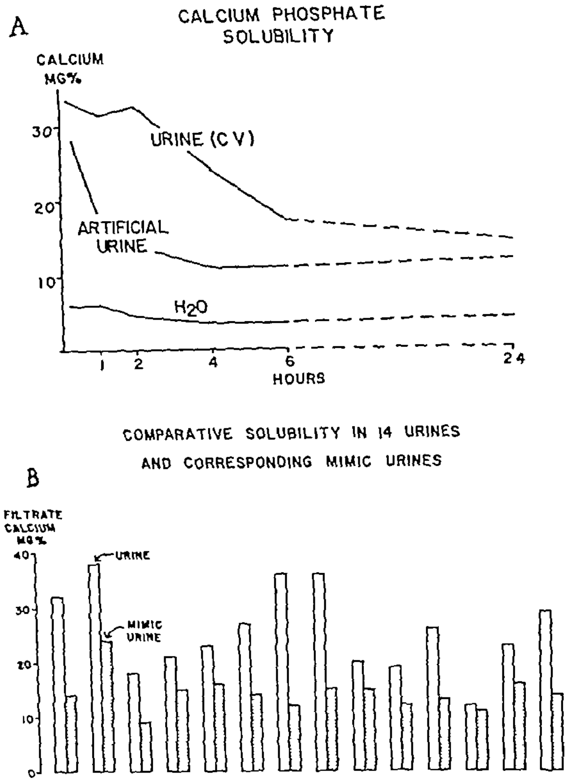

Fig. 3. *A*, solubility in urine, its corresponding mimic urine, and special water control, all with initial pH of 5.65 ± 0.02. Mimic urine was more solubilizing than water but less than real urine, especially during early hours of test. Indicates marked capacity of urine to permit temporary supersaturation.

B, solubility in 14 urines and corresponding mimic urines as judged by calcium levels in filtrates prepared 2 hours after start of test. Urine contains potent solubilizers not present in artificial urine.

ous salts in amounts calculated so that the resulting solution contained the substances just mentioned and in the same concentrations. To get the required salts into solution a small amount of hydrochloric acid was usually necessary. The pH was then accurately adjusted to that of the corresponding actual urine, the greatest deviation being less than 0.1 pH unit. The solubility test was then run on these mimic urines and calcium levels in the filtrates determined at the same time intervals used previously with the actual urines.

In a few instances control tests were performed using distilled water but taking into account the calcium and phosphate initially present in the urine specimens. These water controls were run using more concentrated calcium and phosphate solutions made up so that 1 ml. of each, when added to 10 ml. of water, would give a total concentration equal to the original urine concentration plus that added as precipitants in the previous tests. In this way one may compare the solubility in water with the solubility in fluids that already contain significant amounts of calcium or phosphate.

TABLE 1 *Solubility of calcium phosphate in urine and artificial urine Averages of 14 comparisons*

	Average filtrate calcium in mg %				
	½ hr *	1 hr	2 hr	4 hr	24 hr
Urine	36	33	26	19	17
Artificial urine	30	18	14	14	12
Difference	6	15	12	5	5

* Time is from start of solubility test

Results A representative graph of the results on calcium phosphate solubility is seen in figure 3, *A* With this particular urine the calcium level in the filtrate remained high for the first two hours, only then did it begin to fall significantly Even at six hours it had not reached its ultimate level, indicating marked delay in precipitation The corresponding artificial urine gave very different results At 15 minutes the calcium level was still quite high, but thereafter it fell rapidly so that at two hours it was only one-half of that seen with the actual urine The special water control for this experiment is shown at the bottom of the graph The solubility in water was always considerably less than in the artificial urine, but the actual urine exhibits much greater solubility than the artificial, especially during the early hours of the test Evidently the urine contains additional solubilizers not present in the artificial medium

A total of 14 such observations have been made Table 1 summarizes the results on these 14 urines and corresponding mimic urines giving average values at each of the time intervals studied The difference in the filtrate calcium levels at the two hour interval is shown graphically in figure 3, *B* in each of the 14 instances It is quite evident that real urine is superior to artificial urine in its ability to hold calcium phosphate in solution Urine contains a solubilizing agent not present in the artificial media Various experiments have been done attempting to identify this powerful agent or agents The urines had not been analyzed for carbonate, creatinine, hippuric, or uric acids, therefore additional artificial urines were made up in which arbitrary amounts of these substances were added in relatively high concentrations No appreciable effect was detected with any of them We also thought that the urochromes might possibly act as solubilizers, accordingly tests were run on urine previously shaken with activated charcoal (Norit A) to remove the urochromes The solubility in the colorless urines was no different from that of the untreated specimens

SOLUBILITY IN URINE VERSUS URINE DIALYSATE

Methods The failure of artificial urine to duplicate the solubility in real urine immediately suggests the possibility that the difference might be due to a "protective colloid" action A study of urine dialysates would seem to be a suitable way to test the protective colloid hypothesis since the colloidal substances would not pass through a dialysis membrane Therefore fresh human urines were dialysed by placing 300 ml in a flask and immersing in it a dialysis bag containing 75 ml of water The bag was made of Visking cellulose dialysis tubing 2 cm in diameter and approximately 125 cm in length The tubing was divided into five isolated segments each segment containing 15 ml of water so as to ensure wide distribution and better utilization of the entire surface area A small amount of air was also introduced to facilitate mixing in each segment The flask was shaken on a mechanical shaker for three hours Preliminary studies showed that under these circumstances complete equilibrium of sodium, chloride, and phosphate is rapidly obtained between the fluid inside and outside the dialysis bag As discussed in a previous paper of this series,[9] calcium and citrate dialysed more slowly, but approximate equilibrium for these substances was also attained in 3 hours provided the urine was acid in reaction For this reason, only urines with a pH of 6 or below were selected for this study Upon completion of the 3 hour dialysis period, the pH of the dialysate was always exactly the same as that of the urine The inside and outside fluids are therefore assumed to be identical in all respects except for the non-dialysable components of urine Figure 4 illustrates the conditions before and after dialysis

Results After dialysis, solubility was determined simultaneously in the material inside and outside of the dialysis bags A graph of the results in one experiment is shown in figure 5, which also includes a curve of the solubility in an artificial urine made up to correspond In this experiment solubility in the dialysate was as great as in the urine itself except for a slight reduction at the 4-hour interval A total of 14 such experiments were done The results are shown in figure 6 which compares the filtrate calcium levels two hours after adding the precipitants Very little difference was found between the urines and the corresponding dialysates This is in sharp contrast to the previous study comparing urine with artificial urine as shown in figure 3, *B* Table 2 summarizes the dialysis experiment giving the average values at each of the time intervals studied It may be mentioned that the particular dialysis experiment selected for the graph shown in figure 5 gave the greatest divergence of the entire series It was selected for the illustration not because it was representative but rather to show the instance where the greatest difference occurred between solubility in the urine and its dialysate

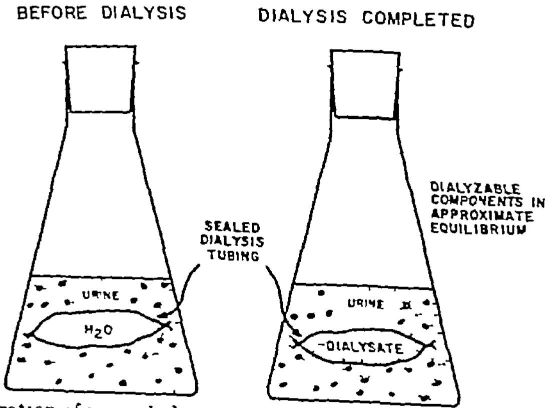

Fig 4 Preparation of urine dialysates Sketch shows condition before and after 3 hours of continuous agitation Solubility will then be compared in dialysate and urine in flask

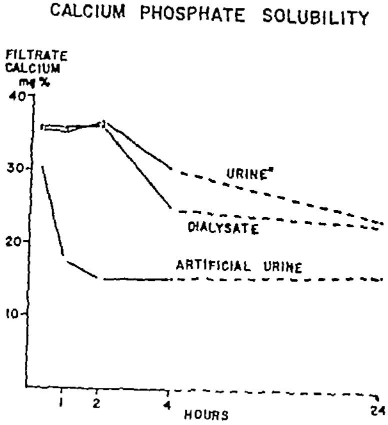

Fig 5 Solubility curves in urine, its dialysate, and corresponding artificial urine, all with initial pH of 5 2 ± 0 01 Solubility in urine and dialysate was much greater than in artificial urine Difference between dialysate and urine shown at 4 hour interval was largest divergence seen in entire series of 14 dialysates tested

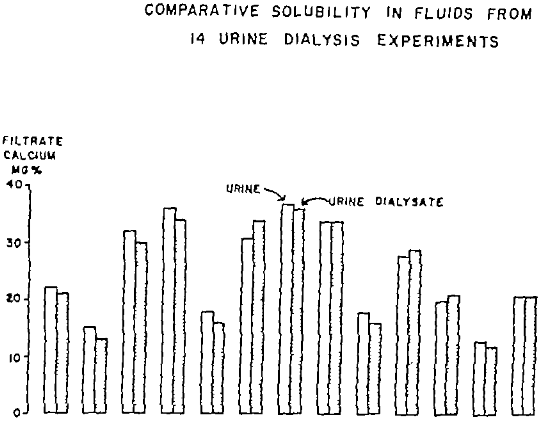

Fig 6 Solubility in 14 urines and corresponding urine dialysates as judged by calcium levels in filtrates prepared 2 hours after start of test Solubility of calcium phosphate in urine dialysates was as great as that in urines from which dialysates were prepared

Table 2 *Solubility of calcium phosphate in urine and urine dialysates Averages of 14 comparisons*

	Average filtrate calcium in mg %				
	¼ hr *	1 hr	2 hr	4 hr	24 hr
Urine	34	30	25	20	20
Urine dialysate	35	29	24	18	18
Difference	1	1	1	2	2

* Time is from start of solubility test

DISCUSSION

This method for testing solubility employs an "ex-solution" technique in which precipitation is induced in a previously clear fluid, thus permitting the possibility of detecting states of supersaturation. With an "in-solution" technique, where the solvent is shaken with the salt in the solid state, information will be obtained only as to saturation, not supersaturation. Study by ex-solution has an additional advantage in that it is more nearly like the process of stone formation in which the salt also passes from the dissolved to the solid state. To a certain extent the test used here may then be looked upon as a simplified model of what goes on in stone formation. But there are obvious and important differences, for instance nothing resembling stone matrix is involved in the model. One needs also to recognize that the precipitate occurring in the test is not of the same composition as the complex apatites found in actual stone salt. A study of the calcium-phosphate ratios indicates that our precipitates initially are composed of $CaHPO_4$ which gradually changes to $Ca_3(PO_4)_2$. If specific solubilizers like magnesium citrate, or the dialysable agent of urine are present, the conversion to the tertiary salt occurs more slowly.

When comparing solubility in different fluids it has already been noted that the initial pH must be identical. But after calcium and phosphate are added, a change in pH will inevitably occur because of the phosphate buffering action. The pH change will vary in different tests because the amount of unprecipitated phosphate will differ depending on the solubility of calcium phosphate. The fluid exhibiting greater solubility will have a higher filtrate phosphate and therefore a somewhat higher filtrate pH—a paradoxical finding when it is remembered that calcium phosphate is more soluble in an acid medium. Actually any precipitation test will encounter the same difficulty when working in the pH range we used. Thus in instances where solubility is increased with this test the increase occurs in spite of a somewhat adverse pH change. A typical example of pH changes is given in the legend of figure 2 A.

This study was undertaken in an effort to explain the supersolubility of calcium phosphate in urine as compared with water at the same pH. A complete explanation was not found. The solubility in urine is considerably greater than in artificial media that mimic the urine in sodium, potassium, calcium, magnesium, sulfate, phosphate, citrate, urea and chloride. Nor did additions of ammonia, carbonate, creatinine, hippuric and uric acids appreciably improve the solubility in the artificial media. All these ions increase solubility by means of the general salt effect, and magnesium and citrate seem to have a special action, but the cumulative effect is not sufficient to explain the observed solubility in urine. The urine apparently contains another substance which greatly augments calcium phosphate solubility. The dialysis experiment shows that the unidentified solubilizer is dialysable and therefore not a protective colloid—if by protective colloid is meant a material which is non-dialysable because it is in a state of colloidal dispersion and which also protects against precipitation of other substances.

The experiments clearly show that urine is capable of maintaining a state of true supersaturation for considerable periods of time By supersaturation we mean a condition in which an excessive amount of the salt temporarily remains dissolved but in an unstable state so that the excess ultimately precipitates out The presence of indifferent ions (like sodium or sulfate) played little or no role in permitting supersaturation though they did serve to increase true solubility On the other hand, magensium and citrate favored a state of supersaturation but not to such a degree as to explain the marked temporary supersaturation seen with urine Urine dialysates behave essentially like whole urine with respect both to true solubility and to supersaturation The extent and duration of the period of supersaturation, as judged by this test, are by no means negligible with regard to the theory of stone formation It needs to be remembered, however, that these experiments study *maximal* supersaturation and not the amount that normally occurs

Since urine contains powerful solubilizers, should diuresis be recommended in an effort to prevent stones? This question arises because diuresis would also dilute the solubilizers, rendering them less effective Experiment has shown the solubility in 10 ml of diluted urine is, indeed, less than in 10 ml of undiluted urine But if 10 ml of urine is diluted with 10 ml of water, tests run on the mixture will show that the *total* amount of calcium phosphate in solution in the 20 ml mixture is greater than that which could be dissolved in 10 ml of the undiluted urine Diuresis, then, though it decreases the amount dissolved per unit volume, is nevertheless advantageous if the increase in total volume is considered

SUMMARY

To study calcium phosphate solubility a technique was used involving precipitation of the salt from the solvent followed by filtration The calcium content in the filtrate was then used as the measure of calcium phosphate still in solution in the solvent Comparisons were made of the solubility in water various water solutions, urine, mimic urine, and urine dialysate The influence of pH on solubility was excluded by equalizing the pH of the fluids prior to running the tests

Marked temporary supersaturation could be produced in urine, often lasting several hours When the period of supersaturation had ended, the true solubility in urine was still much greater than that in water The substances in urine accounting for these differences are

The urinary electrolytes, such as sodium, potassium, chloride, and sulfate They act to increase solubility by a non-specific "salting-in" effect, but play little role in permitting supersaturation

Magnesium and citrate In a way thus far not understood, these materials favor a state of temporary supersaturation if in sufficient concentration

An unidentified solubilizing agent It acts by enhancing both supersaturation and ultimate solubility The unidentified agent is dialysable and hence not colloidal in nature

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CALCIUM OXALATE SOLUBILITY IN URINE: EXPERIMENTAL UROLITHIASIS XIV

G. H. MILLER, C. W. VERMEULEN AND J. D. MOORE

From the Department of Surgery, University of Chicago, Chicago, Ill.

In the preceding paper a brief review was given of the various explanations that have been offered for the apparent supersolubility of the stone-forming salts in urine. For this paper it remains only to add those items from the literature that particularly apply to the urinary solubility of calcium oxalate.

It is universally recognized that calcium and oxalate may be present in urine in higher concentrations than can be obtained even in a completely saturated water solution of calcium oxalate. Differences in pH play little part in explaining this phenomenon because the solubility of calcium oxalate is not significantly increased by the acidity of the medium until it far exceeds that possible in urine. Physical chemical theory immediately suggests the action of the other urinary electrolytes and their "salting-in" effect. Hammarsten[1] has demonstrated that the indifferent ions do indeed influence calcium oxalate solubility. She studied solubility in water and in water solutions of common urinary electrolytes. The method she used consisted of shaking crystalline calcium oxalate in the solvent being studied followed by titration of the dissolved oxalate with permanganate. She found that sodium (either chloride or di-hydrogen phosphate) when present in a concentration comparable to urine increased solubility about three times. Potassium had an equal effect, but magnesium ions had a solubilizing power greater than could be explained by a nonspecific "salting-in" action. Hammarsten therefore postulated the formation of a magnesium-oxalate complex ion to account for this marked solubilizing effect. On the basis of theoretical calculations she concluded that the calcium oxalate solubility in urine could be adequately explained by the general salt effect of the electrolytes in the urine plus the special action of magnesium. Medes,[2] using a similar test method, studied solubility in the presence of urea. She found that 3 gm. per cent urea about doubled the solubility of calcium oxalate.

The literature indicates, then, that for calcium oxalate two mechanisms play a role in increasing solubility in urine—the indifferent salt and urea effect and a special magnesium action. In the experiments here reported an attempt has been made to determine if these actions completely account for the observed concentrations of calcium and oxalate dissolved in the urine or whether other special solubilizing substances or mechanisms have to be considered.

METHODS

Previous workers have employed a technique for studying solubility that involves shaking with powdered calcium oxalate to produce a saturated solution

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[1] Hammarsten, G.: Compt. Rend. Trav. Lab. Carlsberg, 17: [illegible], 19[illegible].

[2] Medes, G.: Proc. Soc. Exp. Biol. and Med., 30: [illegible], 19[illegible].

followed by analysis of the supernatant for oxalate With simple solvents the oxalate is merely titrated with permanganate, but with a complex solvent like urine the oxalate must first be extracted prior to titration, and oxalate extraction is both tedious and inaccurate Therefore a quite different method was used in this study Essentially the test involves two steps The fluid being studied is first accurately adjusted to standard levels of calcium and pH Increments of a standard oxalate solution are now added until a precipitate of calcium oxalate appears If other conditions are controlled, the amount of oxalate required to produce a precipitate is an index of the solubility

Preparation of solutions for testing All fluids to be tested are adjusted to contain 15 mg per cent calcium by adding the appropriate amount of a concentrated solution of calcium carbonate in dilute acid (240 mg per cent Ca) When solubility in urine is being studied, it is first necessary to determine its calcium content and add the calculated amount to bring the total to 15 mg per cent calcium (Urines already containing more than this amount were necessarily discarded from this study) The pH is now adjusted to 6 0 with dilute sodium hydroxide using a glass electrode pH meter Thereafter the fluid is passed through fine Buchner fritted glass funnels to remove any dust or lint particles which might later interfere in the test

Testing for solubility Five ml of the prepared fluid are introduced into a series of Coleman tubes by means of a burette To the first tube of the series, 2 ml of distilled water are now added, and decreasing amounts to the remaining tubes, each tube receiving 0 1 ml less than the preceding After mixing, additions of sodium oxalate solution (0 005M) are made to all except the first tube of the series The second tube receives 0 1 ml of the oxalate and each tube thereafter receives increasing amounts in increments of 0 1 ml When all additions have been made, the total volume is 7 ml in each tube The contents are now mixed and the tubes allowed to stand for one-half hour They are then examined for the presence or absence of precipitate by means of a Coleman nephelometer This instrument can detect suspended particulate matter at levels far below that which can be seen with the naked eye Its extreme sensitivity is the reason why scrupulous attention must be given to cleanliness and removal of dust particles by special filtration before the test is run Any tube giving a reading of 10 or above on the nephelometer scale (a level not visible to the naked eye) is taken as indicating the presence of precipitate The nephelometer is not used to determine *amounts* of precipitate but merely its presence or absence in any given tube The first tube of the series that shows a precipitate is taken as the endpoint, and the amount of oxalate that had been added to it is used as the index of solubility of calcium oxalate in the fluid being examined The tubes preceding it in the series will show no precipitate because they are unsaturated, the tubes following it will show progressively more and more precipitate since greater and greater amounts of oxalate are present

Using the above test, solubility was first determined in simple water solutions of some of the constituents ordinarily found in urine The test was then used to determine the solubility in various normal urine specimens and corresponding mimic urines prepared in the manner described in the preceding paper in this series

RESULTS

Preliminary experiments showed that changes in pH within the range commonly found in urine did not greatly alter the solubility of calcium oxalate It will be remembered that in the previous study with calcium phosphate the factor of time was of considerable importance Therefore a study of the time relations in oxalate precipitation was also done but it was found to be of little importance beyond a certain minimal interval Readings taken 15 minutes after the addition of the oxalate solution were the same as those taken 24 hours later Consequently, the tests were all arbitrarily run at a pH of 6 0 and read at one-half hour

Figure 1 gives the results of the tests on pure solutions Creatinine (87 mg per cent) and hippuric acid (70 mg per cent) had no effect in increasing solubility Urea (3 gm per cent), sodium sulfate (266 mg per cent) and sodium di-hydrogen phosphate (172 mg per cent) all showed slight solubilizing action Magnesium chloride (32 mg per cent) produced a marked increase in oxalate solubility thus confirming Hammarsten's observations on solubilizing by magnesium ions Sodium chloride (2 gm per cent) was quite effective because of the relatively high concentration used As expected, citric acid (100 mg per

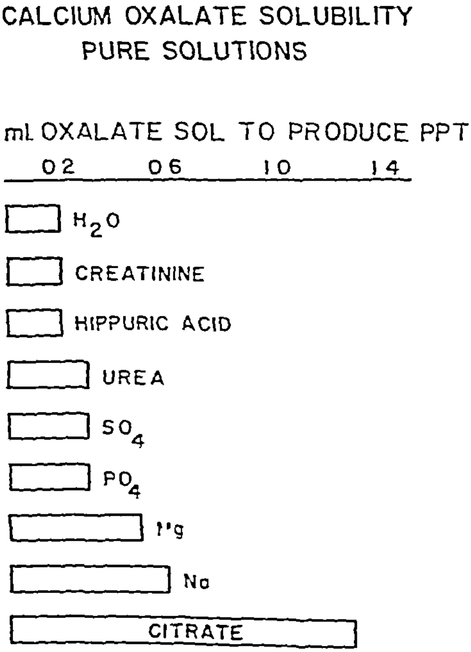


Fig 1 Solubility of calcium oxalate in simple solutions and water as measured by test described in text Urea sulfate and phosphate increased solubility moderately Magnesium sodium and especially citrate increased solubility considerably Concentrations used were arbitrarily chosen as representing high normal values for urine

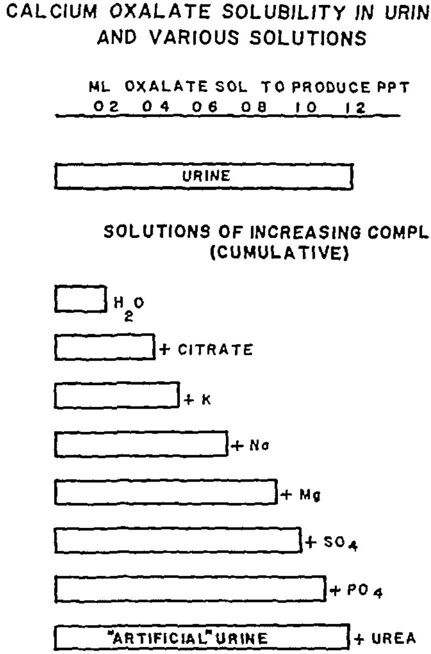


FIG 2 Solubility in a urine compared with solubility in solutions prepared to match concentration of original urine in substances indicated Note that as solutions become more complex, calcium oxalate solubility increases until it equals that of original urine when all indicated ions etc are present

cent) markedly increased the oxalate solubility because of its calcium-complexing properties It should be mentioned that each of these tests was run three or more times with identical results

It is therefore evident that the common constituents of urine do indeed increase the solubility of calcium oxalate over that in water How effective are these actions in urine? To answer this question fresh normal urines were studied for solubility and at the same time analyzed for citrate, sodium, magnesium, potassium, sulfate, phosphate, and urea Equivalent solutions were then prepared to mimic the urine The results of one such experiment are shown in figure 2 In this particular study the solubility was determined in a series of solutions, each one progressively more complex than the preceding As the number of ingredients increased, the solubility of calcium oxalate also progressively increased We have called the most complex solution "artificial urine" It contained citrate, potassium, sodium, magnesium, sulfate, phosphate, and urea, all in the same concentration as had been found in the parent urine (Of course the anions and cations did not balance, it was therefore necessary to use chlorides to supply part of the anionic components) With this artificial urine the solubility of calcium oxalate was exactly the same as in the parent urine

Similar experiments were run on a total of 13 fresh normal urines In only one instance did the oxalate solubility in the artificial urine fail to approximate that in the original urine Figure 3 is a graph of the averaged results of these 13 experiments The solubility in the artificial urines, if anything, appeared to be a

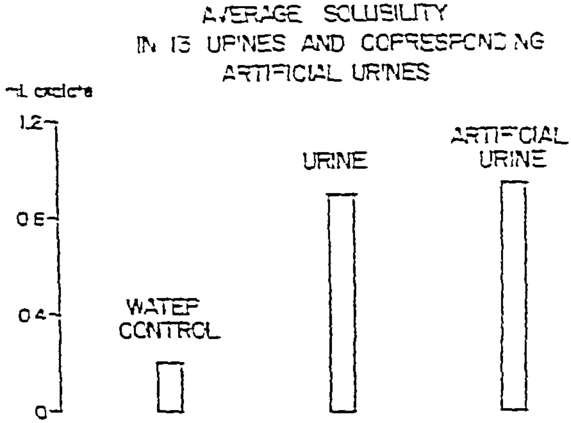


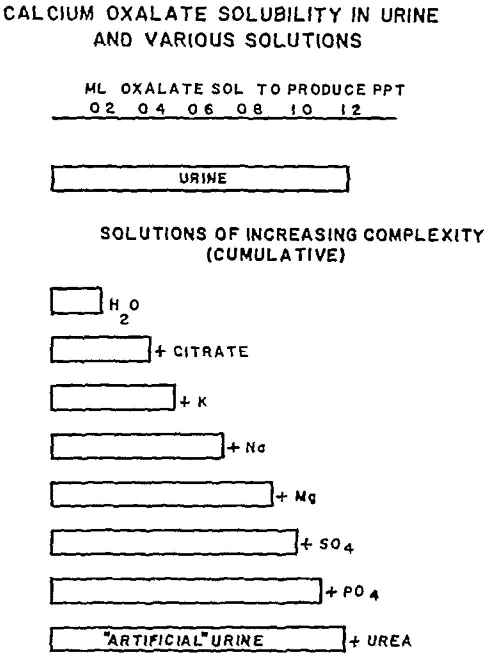
Fig. 3. Averages of 13 examinations comparing solubility in 13 normal urine specimens and corresponding artificial urines. Water control for comparison.

little better than in the original urines. It must be noted that in running tests on urine the oxalate already present in the specimen will alter the results somewhat. In some of the earlier tests this was not taken into consideration. With later specimens, however, oxalate determinations were done and oxalate included in constructing the artificial urines. Ordinarily the amount of oxalate present made a slight though distinct difference in the results obtained.

DISCUSSION

One advantage of the test method used here has already been mentioned, that is, it avoids oxalate determinations by a tedious and inaccurate extraction with ether. It has another advantage in that it employs the "ex-solution" rather than the "in-solution" process. It therefore offers the possibility of detecting states of supersaturation and the influence of time on precipitation of calcium oxalate. But it also has a disadvantage in that the exactness of the result is limited by the size of the oxalate increments added to the successive tubes. We learn only that the true point of saturation lies somewhere between one tube showing no precipitate and the next one in the series that does. If the difference in the amount of oxalate used in the two tubes is large, the exact point of saturation becomes correspondingly indefinite. For our purposes it would appear that the oxalate increments used by us were sufficiently small to give the desired information. At first sight the test sounds cumbersome but with experience and scrupulous attention to detail we believe it can give information far more easily than other methods, particularly when studying solubility in fluids where direct permanganate titration of the oxalate cannot be used.

The results confirm the well-known observation that calcium and oxalate may be present in the urine in much higher concentrations than in a completely saturated solution of calcium oxalate in water. The pH plays only a very minor role in permitting this relative supersolubility. In contrast to phosphate, true supersaturation with calcium oxalate was not found and the solubility in urine



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DIAMOX AS AN AID IN THE COLLECTION OF URETERAL SPECIMENS

P. K. RATLIFF AND S. L. FELLMAN

Valuable information can be derived from the examination of split urine specimens obtained by ureteral catheters. Such examinations may include bacteriologic, pathologic, microscopic and biochemical determinations. The ease with which such specimens are obtained is dependent upon the patient having an adequate urine output.

Most retrograde studies at Ann Arbor hospitals are performed under general anesthesia which precludes the patient ingesting a large volume of fluid on the morning of endoscopy. Other methods have been used to provide the necessary diuresis. Fluids have been forced hourly on the night preceding the examination, but this is an obvious inconvenience to both patients and nursing staff. Another method is to begin an intravenous infusion of glucose solution run at a rapid rate an hour prior to the procedure. This has obvious drawbacks in terms of time consumption, cost and inconvenience.

A preferable method would appear to be the administration of a safe, low cost and rapid acting diuretic as part of the anesthetic premedication. Diamox appeared to fulfill these requirements. While the efficacy of diamox as a diuretic in normally hydrated or edematous patients is well known, its efficacy in dehydrated, preanesthetic patients had to be determined.

Such a study was performed as follows. Patients with indwelling catheters were prepared as for morning anesthesia, that is, they were allowed no food or fluid from midnight on. Two 30-minute urine collections were taken beginning at 7 a.m. as controls. At 8 a.m. each patient was given a 250 mg. diamox tablet with only enough water to permit swallowing of the tablet. Fifteen minute urine collections were then taken for two and one-half hours.

The onset of diuresis is at approximately forty-five minutes and persists for approximately an additional hour and one-half. The peak of the diuretic curve is in the 60 to 90-minute period. Thus the drug may efficiently be a part of the preanesthetic medications usually given 45 minutes to one hour prior to anesthesia.

The average urine flow during the 60 to 90-minute period was 2.5 cc per minute compared to a basal urine output of less than 0.7 cc per minute in the dehydrated patient. In all instances the urine output was at least doubled and in most cases quadrupled or more.

To provide actual clinical application of this premise, split urine outputs have been determined in patients under anesthesia and with the insertion of ureteral catheters following premedication with diamox. In all instances the urine output has been sufficient to permit the rapid collection of split specimens.

In summation, the use of diamox in the dosage of 250 mg. administered orally one hour prior to ureteral catheterization is suggested as an aid in the rapid collection of split urine specimens.

326 North Ingalls St., Ann Arbor, Mich.

Read at annual meeting of North Central Section of American Urological Association, Mackinac Island, Mich., August 29–31, 1957.

could be entirely explained on the basis of the nonspecific salt effect plus the special complexing action of citrate and magnesium Artificial urines gave the same solubility as the corresponding actual urines if the mimic urines contained the same amount of the various electrolytes, urea, citrate, and magnesium The special action of citrate is undoubtedly due to its ability to complex with calcium, the magnesium action is probably to be explained, as Hammarsten suggested, by its ability to complex with oxalate The artificial media did not contain any "protective colloid" materials and there seems, therefore, no need to consider such a colloidal mechanism to explain the solubility of calcium oxalate in urine Others have reached the same conclusion based upon theoretical calculations but to our knowledge this is the first time an attempt has been made to actually compare the solubility in urine and mimic media by empiric test The result with both calcium phosphate and oxalate has been a failure to find evidence for a protective colloid mechanism

SUMMARY

A precipitation test was developed to study calcium oxalate solubility in pure solutions, urine, and solutions made up to mimic the urines tested

Calcium oxalate was found to be supersoluble in urine as compared with water The supersolubility could be adequately explained by the "salting-in" effect of the urinary electrolytes and the formation of two complex ions The urinary colloids were not necessary to explain the observed solubility of calcium oxalate in urine

Modern Concepts of Urologic Endocrinology M M Steiner, Chicago, Ill

A Hypospadias Repair with Placement of Urethral Meatus in Glans Penis S H Johnson III and (by invitation) Matthew Marshall, Jr, Pittsburgh Pa
Discussion O S Culp Rochester, Minn

Reoperative Correction of Previous Ureteropelvic Plastic Surgery D C Malcolm and J W Dorsey, Long Beach Calif
Discussion F E B Foley St Paul Minn

Anterior Sacral Meningocele with Pathognomonic Sacral Defect J W Pick (by invitation) and C P Marquardt Milwaukee Wis
Discussion Homer Kirgis (by invitation) New Orleans, La

Motion Pictures 2 00 p m. to 5 00 p m

Transperitoneal Nephrectomy Hardy Ulm, New York, N Y

Pyelo Ureterography by Percutaneous Puncture Gustavo Calle Uribe (by invitation) Medellin Colombia S A

Plastic Repair of Exstrophy with Bilateral Osteotomy of Ilia W G Shultz, Tucson, Ariz

Surgical Preservation of Renal Function in Exstrophy W H Boyce, Winston-Salem, N C and S A Vest Charlottesville Va

Technique of the Gersuny Operation for Exstrophy Frank Hinman, Jr and (by invitation) Richard Gardner San Francisco Calif

Operation for Exstrophy of Urinary Bladder W E Goodwin and (by invitation) C C Winter and R D Turner, Los Angeles Calif

Radical Penectomy for Carcinoma E P DePosa Chicago Ill

Partial Replacement of Tuberculous Ureter and Bladder Utilizing a Segment of Ileum J K Lattimer and (by invitation) Anthony Spirito, Louis Spivack and Herman Wechsler New York N Y

Revascularization of the Kidney Utilizing an Isolated Loop of Ileum (Experimental Study) B S Abeshouse and (by invitation) P Goldstein Baltimore Md

Excision of Diverticulum of Renal Pelvis Gilbert Ottenberg J G Lewis and (by invitation) P E Byrne Washington D C

Wednesday April 30

Motion Pictures 8 00 a.m. to 9 00 a.m.

Repair of Urethrorectal Fistula J W Merricks Chicago, Ill

Transperitoneal Bilateral Lymphadenectomy for Testis Tumor J F Patton and (by invitation) Nicholas Mallis Washington, D C

Subtotal Cystectomy for Carcinoma of Urinary Bladder R C Baker Washington D C

Scientific Sessions 9 00 a.m. to 12 30 p m.

Transurethral Resection of Female Bladder Neck N B Powell and (by invitation) L B Powell Houston Tex
Discussion Hugh J Jewett Baltimore Md

The Journal of Urology
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PROGRAM, ANNUAL MEETING OF AMERICAN UROLOGICAL ASSOCIATION, INC , APRIL 28–MAY 1, 1958, THE ROOSEVELT HOTEL, NEW ORLEANS, LA

Monday, April 28

Scientific Sessions 9 00 a m to 12 noon

Technique and Results of Ileocystoplasty and Sigmoidocystoplasty W E Goodwin and (by invitation) C C Winter and R D Turner, Los Angeles, Calif

Functional Characteristics of the Ileal Segment as a Valve Frank Hinman, Jr and *(by invitation) Rudolf Oppenheimer, San Francisco, Calif*

Primary Diversion of Hydronephrotic Kidney to an Ileal Conduit A Murphy (by invitation), J J Lee and (by invitation) L M King, Pittsburgh, Pa
Discussion J J Cordonnier, St Louis, Mo

Management of Recurrent Infections of Genito-Urinary Tract in Infants and Children F B Bicknell, Detroit, Mich

Operative Correction of Vesico Ureteral Reflux in Non Paraplegic Child Indications, Technique and Results Foster Fuqua, J C Alexander, K B King and (by invitation) E W Ware, Jr
Discussion Meredith F Campbell, Miami, Fla

Interstitial Cystitis in Children H P McDonald, Atlanta, Ga

Ureteral Ectopia H D Woodson and A L Herring, Memphis, Tenn
Discussion H M Spence, Dallas, Tex

Tuesday, April 29

Motion Pictures 8 00 to 9 00 a m

Tricks of the Trade E W Brown, West Palm Beach, Fla

Parasacral Prostatectomy B S Vallett, Wilmington, Del

Simplified Method of Perineal Prostatectomy B S Abeshouse, Baltimore, Md

Scientific Sessions 9 00 a m to 12 30 p m

Exfoliated Cytology of Urinary Tract A New Approach with Particular Reference to the Collection of Material and Preparation of Slides for Study R D Amelar and Cyril Solomon (by invitation), R M Hyman and (by invitation) Robert Chaiban, New York, N Y

The Voluntary Control of Micturition S R Muellner, Boston, Mass

Structure and Function of Internal Vesical Sphincter Clinical Applications *Jack Lapides (by invitation), Ann Arbor, Mich*

The Relative Importance of Venous and Lymphatic Routes from Renal Pelvis to Circulating Blood Theodore Bledsoe and J J Murphy (by invitation), Philadelphia Pa

Maximum Clearances (GFR and ERPF) in Dogs W S Kerr, Jr , Boston, Mass

Occurrence of Fibrinolysin During Transurethral Prostatic Surgery William Baurys and (by invitation) Horace Jacobson, Sayre, Pa
Discussion W P Herbst, Jr , Washington, D C

Urologic Pitfalls in Management of Carcinoma of Cervix C J E Kickham, Brookline, Mass

Ureteral Obstruction Due to Carcinoma of Rectosigmoid or Its Metastases C N Burns and P P Mayock Wilkes-Barre, Pa
Discussion H T Beacham, New Orleans, La

Solitary Distant Metastases from Unsuspected Renal Carcinoma Richard Chute and (by invitation) E F Ireland, Jr and J D Houghton, Brookline, Mass
Discussion V F Marshall, New York, N Y

Spontaneous Rupture of Renal Pelvis W E Forsythe W L Huffman and (by invitation) Lester Persky, Cleveland Ohio
Discussion T R Montgomery, Portland, Ore

2 00 p m to 5 00 p m

Panel Discussion Medicolegal Aspects of Urology Moderator, Hubert Winston Smith Director and Professor of Law and Legal Medicine, Law Science Institute, University of Texas, Austin, Tex , C D Creevy, Director of Urology in the Department of Surgery, Medical School of the University of Minnesota, Minneapolis, Minn , Charles Montgomery Stewart, Associate Clinical Professor of Urology, University of Southern California, School of Medicine, Los Angeles, Calif Leonard Paul Wershub, Associate Professor of Urology, New York Medical College, Metropolitan Medical Center, New York N Y , Alvin Christovich, head of the Legal Department of the New Orleans Public Service, New Orleans, La

Transperitoneal Bilateral Lymphadenectomy for Testis Tumor New Surgical Approach Nicholas Mallis (by invitation) and J F Patton, Washington, D C
Discussion L G Lewis, Washington, D C

Wilms Tumor Report of Sixty Cases J K Lattimer, M M Melicow and (by invitation) Aurelio Uson, New York, N Y
Discussion S N Vose, Boston Mass

SCIENTIFIC EXHIBITS*

Dr Samuel A Vest, *Chairman*

Genitourinary Tumors in Children Armed Forces Institute of Pathology (F K Mostofi and by invitation, E A Theiss), Washington D C

Some Contributions of Dr Hugh H Young to Operative Urology Armed Forces Institute of Pathology (W M Silliphant Capt MC USN, by invitation and E E Ferguson) Washington D C

The Seminal Vesicles Before and After Open Prostatectomy J H Arnold (by invitation) Houston Texas

Subtotal Cystectomy in Treatment of Bladder Cancer Roger Baker and (by invitation) Timothy Kelly Charles Putnam Timothy Tehan and Edouard Beaugard, Washington D C

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* As of February 8 1958 *Editor*

EFFECTS OF PROLONGED URETHRAL CATHETERIZATION I PERSISTENCE OF NORMAL RENAL STRUCTURE AND FUNCTION H S Talbot and (by invitation) E M Mahoney and S R Jaffee, West Roxbury, Mass
Discussion R C Bunts, Richmond, Va

CLINICAL REVIEW OF ONE THOUSAND CONSECUTIVE RETROPUBIC PROSTATECTOMIES G D Blue and J M Campbell (by invitation), Saskatoon, Canada
Discussion Robert Lich, Jr , Louisville, Ky

URO-EPITHELIUM TRANSPLANTATION TO INTESTINAL SEGMENTS AN EXPERIMENTAL STUDY (First Prize, Essay Contest) Michel Gilbert, W G Pace, III and R J Izant, Jr (by invitation), Columbus, Ohio

PANEL DISCUSSION DETERMINATION OF SEX AND WHAT TO DO ABOUT IT Moderator, Raymond G Bunge, Professor of Urology, College of Medicine, State University of Iowa, Iowa City, Ia , Alexander Albert, Professor of Physiology, Mayo Foundation, University of Minnesota and head of Endocrinological Laboratory, Mayo Clinic, Rochester, Minn , Edgar Burns, Professor of Urology, Tulane University School of Medicine, and head of Department of Urology, Ochsner Clinic, New Orleans, La , and Joan G Hampson, Assistant Professor of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Md

2 00 p m to 5 00 p m

PRESIDENT'S ADDRESS OFFICE UROLOGY W J Baker, Chicago, Ill

THE RAMON GUITERAS LECTURE AN EVALUATION OF CYSTECTOMY IN UROLOGIC SURGERY C C Higgins, Cleveland, Ohio

THURSDAY, MAY 1

Motion Pictures 8 30 a m to 9 30 a m

OPERATION FOR HYPOSPADIAS S H Johnson, III, Pittsburgh, Pa

RETROPUBIC PROSTATOVESICULECTOMY McCleery Glazier and (by invitation) L J Lombardo, Los Angeles, Calif

TOTAL PROSTATECTOMY AFTER PRELIMINARY LIGATION OF VASCULAR PEDICLE E W Campbell, Philadelphia, Pa

RADICAL RETROPERITONEAL LYMPH NODE RESECTION FOR CARCINOMA OF PROSTATE R H Flocks, Iowa City, Ia

Scientific Sessions 9 30 a m to 12 30 p m

STUDIES IN UROLITHIASIS V SALICYLATE THERAPY FOR CALCIUM URINARY STONE PROGRESS REPORT E L Prien, Brookline, Mass and (by invitation) W O Foye, Boston Mass
Discussion C W Vermeulen, Chicago, Ill

PERISTALSIS OF URETER AFTER SURGERY S R Weinberg and (by invitation) A A Siebens, Brooklyn, N Y
Discussion T E Gibson, San Francisco, Calif

CONGENITAL VASCULAR TUMORS AND MALFORMATIONS INVOLVING URINARY TRACT DIAGNOSIS AND SURGICAL MANAGEMENT J B Hamsher and Turley Farrar (by invitation) and T D Moore, Memphis, Tenn
Discussion G J Bulkley Chicago, Ill

UNEXPLAINED HEMORRHAGE IN UROLOGIC SURGERY W A Barrett and (by invitation) Glenn Reid, Pittsburgh Pa

Occurrence of Fibrinolysis During Transurethral Prostatic Surgery William Baurys and (by invitation) Horace Jacobson Sayre, Pa
Discussion W P Herbst Jr , Washington, D C

Urologic Pitfalls in Management of Carcinoma of Cervix C J E Kickham, Brookline Mass

Ureteral Obstruction Due to Carcinoma of Rectosigmoid or Its Metastases C N Burns and P P Mayock Wilkes-Barre, Pa
Discussion H T Beacham New Orleans La

Solitary Distant Metastases from Unsuspected Renal Carcinoma Richard Chute and (by invitation) E F Ireland Jr and J D Houghton, Brookline, Mass
Discussion V F Marshall, New York N Y

Spontaneous Rupture of Renal Pelvis W E Forsythe W L Huffman and (by invitation) Lester Persky, Cleveland Ohio
Discussion T R Montgomery, Portland, Ore

2 00 p m to 5 00 p m

Panel Discussion Medicolegal Aspects of Urology Moderator, Hubert Winston Smith Director and Professor of Law and Legal Medicine Law Science Institute, University of Texas Austin, Tex , C D Creevy, Director of Urology in the Department of Surgery Medical School of the University of Minnesota, Minneapolis, Minn , Charles Montgomery Stewart, Associate Clinical Professor of Urology University of Southern California School of Medicine Los Angeles Calif Leonard Paul Wershub, Associate Professor of Urology, New York Medical College Metropolitan Medical Center, New York N Y , Alvin Christovich, head of the Legal Department of the New Orleans Public Service, New Orleans La

Transperitoneal Bilateral Lymphadenectomy for Testis Tumor New Surgical Approach Nicholas Mallis (by invitation) and J F Patton, Washington, D C
Discussion L G Lewis Washington D C

Wilms Tumor Report of Sixty Cases J K Lattimer, M M Melicow and (by invitation) Aurelio Uson New York N Y
Discussion S N Vose Boston Mass

SCIENTIFIC EXHIBITS*

Dr Samuel A Vest, *Chairman*

Genitourinary Tumors in Children Armed Forces Institute of Pathology (F K Mostofi and, by invitation E A Theiss), Washington D C

Some Contributions of Dr Hugh H Young to Operative Urology Armed Forces Institute of Pathology (W M Silliphant Capt MC USN, by invitation and E E Ferguson) Washington D C

The Seminal Vesicles Before and After Open Prostatectomy J H Arnold (by invitation) Houston Texas

Subtotal Cystectomy in Treatment of Bladder Cancer Roger Baker and (by invitation) Timothy Kelly Charles Putnam Timothy Tehan and Edouard Beaugard Washington D C

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* As of February 8 1958 *Editor*

Effects of Prolonged Urethral Catheterization I Persistence of Normal Renal Structure and Function H S Talbot and (by invitation) E M Mahoney and S R Jaffee, West Roxbury, Mass
Discussion R C Bunts, Richmond, Va

Clinical Review of One Thousand Consecutive Retropubic Prostatectomies G D Blue and J M Campbell (by invitation), Saskatoon, Canada
Discussion Robert Lich, Jr , Louisville, Ky

Uro-Epithelium Transplantation to Intestinal Segments An Experimental Study (First Prize, Essay Contest) Michel Gilbert, W G Pace, III and R J Izant, Jr (by invitation), Columbus, Ohio

Panel Discussion Determination of Sex and What to do About It Moderator, Raymond G Bunge, Professor of Urology, College of Medicine, State University of Iowa, Iowa City, Ia , Alexander Albert, Professor of Physiology, Mayo Foundation, University of Minnesota and head of Endocrinological Laboratory, Mayo Clinic, Rochester, Minn , Edgar Burns, Professor of Urology, Tulane University School of Medicine, and head of Department of Urology, Ochsner Clinic, New Orleans, La , and Joan G Hampson, Assistant Professor of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Md

2 00 p m to 5 00 p m

President's Address Office Urology W J Baker, Chicago, Ill

The Ramon Guiteras Lecture An Evaluation of Cystectomy in Urologic Surgery C C Higgins, Cleveland, Ohio

Thursday, May 1

Motion Pictures 8 30 a m to 9 30 a m

Operation for Hypospadias S H Johnson, III, Pittsburgh, Pa

Retropubic Prostatovesiculectomy McCleery Glazier and (by invitation) L J Lombardo, Los Angeles, Calif

Total Prostatectomy after Preliminary Ligation of Vascular Pedicle E W Campbell, Philadelphia, Pa

Radical Retroperitoneal Lymph Node Resection for Carcinoma of Prostate R H Flocks, Iowa City, Ia

Scientific Sessions 9 30 a m to 12 30 p m

Studies in Urolithiasis V Salicylate Therapy for Calcium Urinary Stone Progress Report E L Prien Brookline, Mass and (by invitation) W O Foye, Boston, Mass
Discussion C W Vermeulen, Chicago, Ill

Peristalsis of Ureter after Surgery S R Weinberg and (by invitation) A A Siebens, Brooklyn, N Y
Discussion T E Gibson, San Francisco, Calif

Congenital Vascular Tumors and Malformations Involving Urinary Tract Diagnosis and Surgical Management J B Hamsher and Turley Farrar (by invitation) and T D Moore Memphis, Tenn
Discussion G J Bulkley, Chicago, Ill

Unexplained Hemorrhage in Urologic Surgery W A Barrett and (by invitation) Glenn Reid, Pittsburgh, Pa

Composition and Structure of Urinary Calculi W H Boyce, J S King (by invitation) and F K Garvey, Winston-Salem, N C

Devices for Improved Technique of Bladder Irrigation at Patient's Bedside, Mechanical Operation of Drainage Tray of Cystoscopic Table Balance Arm for Cystoscopic Table and Attachment for Cystoscopic Table for Irrigating Flask E W Brown, West Palm Beach, Fla

Wirt B Dakin Historical Museum of the American Urological Association W B Dakin, Los Angeles, Calif

Bone Formation in Experimental Pyeloureteroneostomy J W Draper and (by invitation) J M Pearce and R W Lavengood, Jr , New York, N Y

Evaluation of Hypospadias in Intersex Problems Harry Grabstald, M K O'Heeron and (by invitation) George Clayton, J D Smith and J R Fish, Houston, Texas

Anastomosis of the Ureter New Technique F C Hamm and S R Weinberg, Brooklyn, N Y

Sex Chromatin in Prostatic Tumors T H Lehman and Abe Oyamada (by invitation), and C V Hodges, Portland, Ore

The Ileal Segment as a Valve Frank Hinman, Jr and (by invitation) Rudolf Oppenheimer, San Francisco, Calif

Tissue Diagnosis of Curable Prostatic Cancer P B Hudson, New York, N Y

Alm Roentgenograms of Surgically Exposed Kidney C R Marquardt and (by invitation) J W Pick, Milwaukee, Wis

Carbon Dioxide for Presacral Pneumography A Safe Technique R R Landes and (by invitation) C L Ransom and Robert McLelland, Danville, Va

Abdominal Masses in Children M M Melicow and (by invitation) A C Uson, New York, N Y

Needle Biopsy of Prostate Sam Peck, San Diego, Calif

Anterior Sacral Meningocele with Pathognomonic Sacral Defect J W Pick (by invitation) and C R Marquardt, Milwaukee, Wis

Volumetric, Gravimetric and Radioisotopic Determination of Fluid Transfer in Transurethral Prostatectomy R O Taylor (by invitation) E S Maxson (by invitation), F H Carter (by invitation), William Bethard (by invitation) and R J Prentiss, San Diego, Calif

Urinary Calculus Mechanisms of Formation, Structure Studies E L Prien Brookline, Mass

A New Urographic Method for Determination of Voiding Efficiency M S Roberts (by invitation), J K Lattimer and (by invitation) Hans Zinsser and Donald Johnson New York, N Y

Retropubic Y Plasty for Vesical Neck Obstruction T J Sinatra (by invitation), New York, N Y

Regional Renal Hypothermia Paul Stueber and Lester Persky (by invitation) Cleveland, Ohio

Uses of Isolated Segments from Intestinal Tract in Genitourinary Surgery R D Turner (by invitation), Los Angeles, Calif

Nonvenereal Diseases of the Genitals The Differential Diagnosis of Genital Lesions J F Wilson (by invitation), Philadelphia, Pa

A New Isotope Test for Vesico Ureteral Reflux C C Winter (by invitation), Los Angeles, Calif

Exfoliative Cytology of Senile Female Urethra N H Youngblood and (by invitation) E M Tomlin and J O Williams Concord, N C

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Parke Davis & Company Detroit Mich	9
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Mid Atlantic—Richmond Va October 1, 2, 3, 4, 1958
North Central—Schroeder Hotel, Milwaukeee Wis, October 7, 8, 9, 10, 1958
Northeastern—Equinox House Manchester, Vt, September 10, 11, 12 13 1958
South Central—Dallas Texas October 12 13 14, 15 1958
Southeastern—Brown Hotel Louisville, Ky, April 29–May 2, 1959
Western—Monterey, Calif, May 18, 19, 20, 21, 1959

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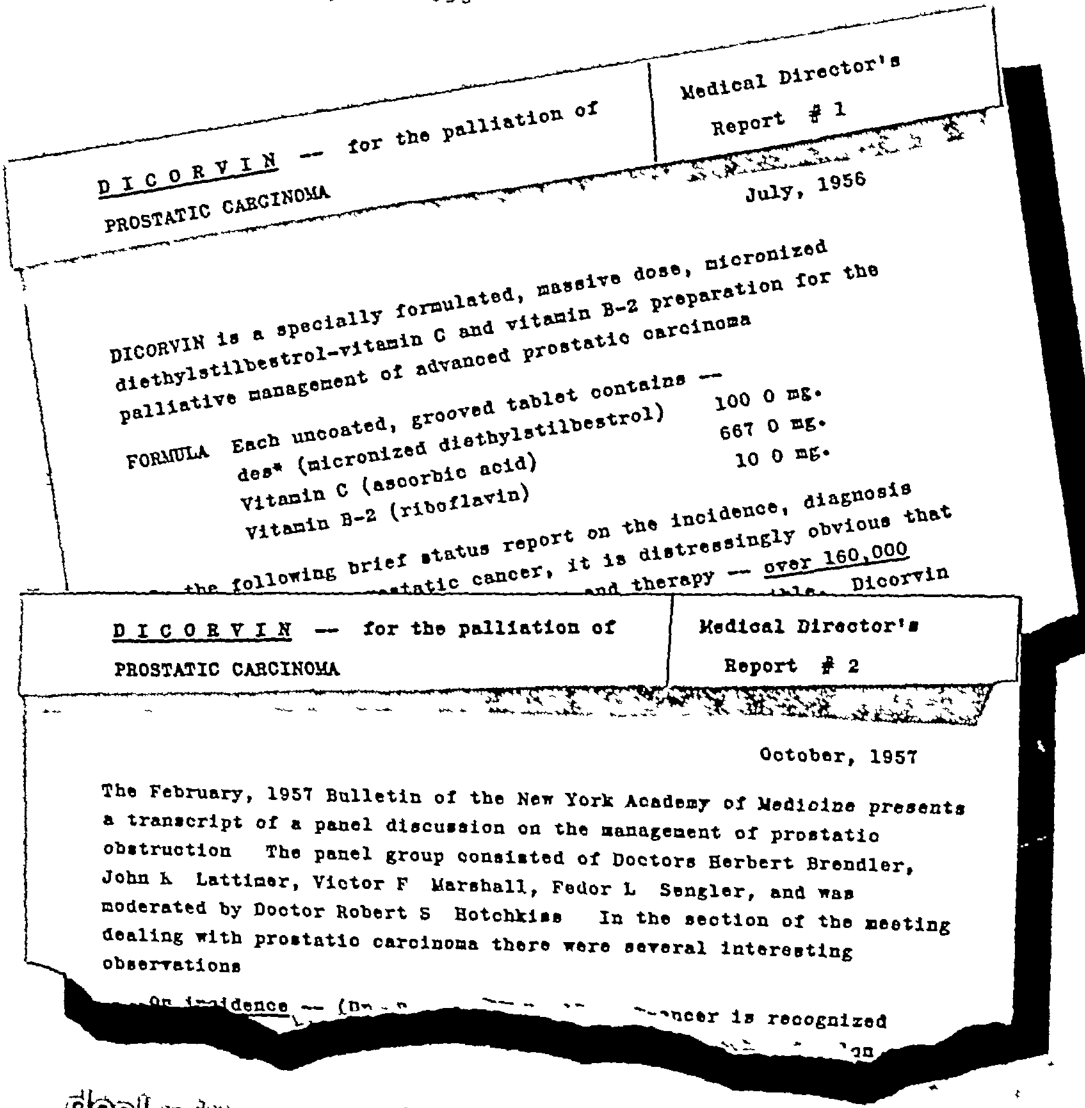

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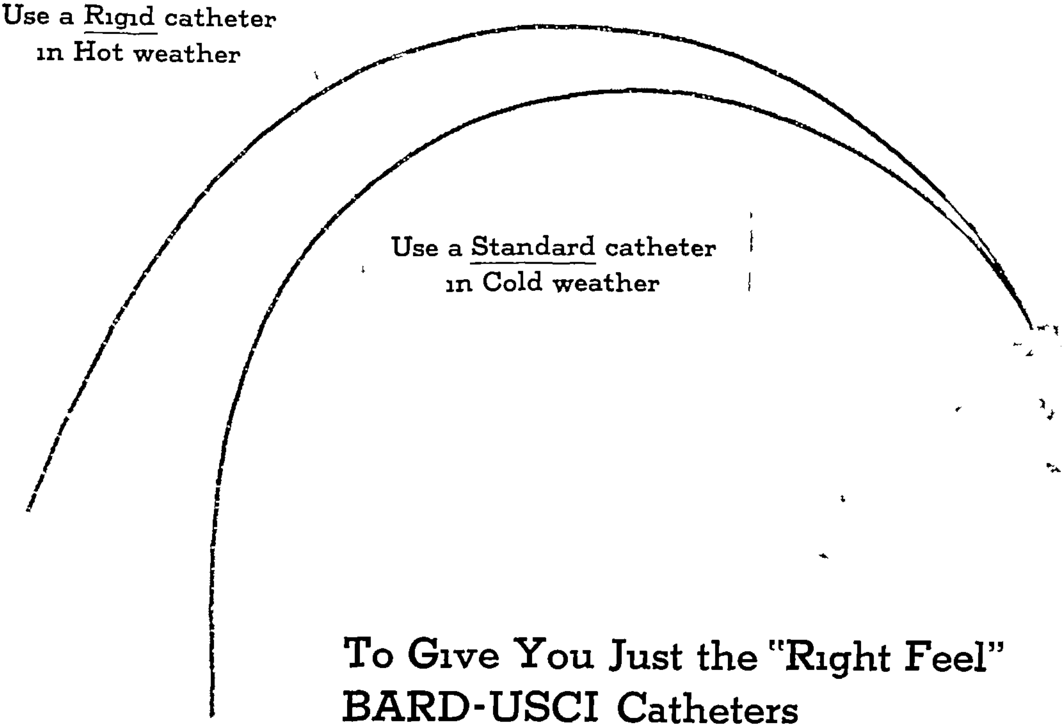

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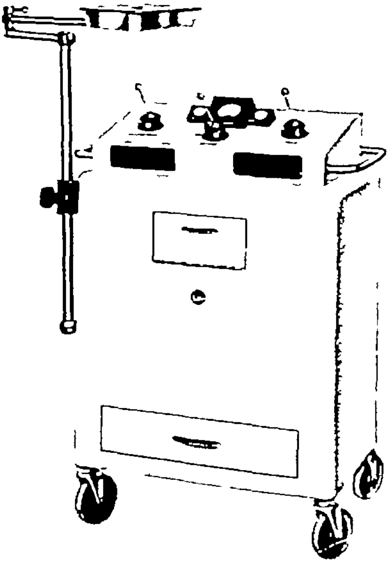

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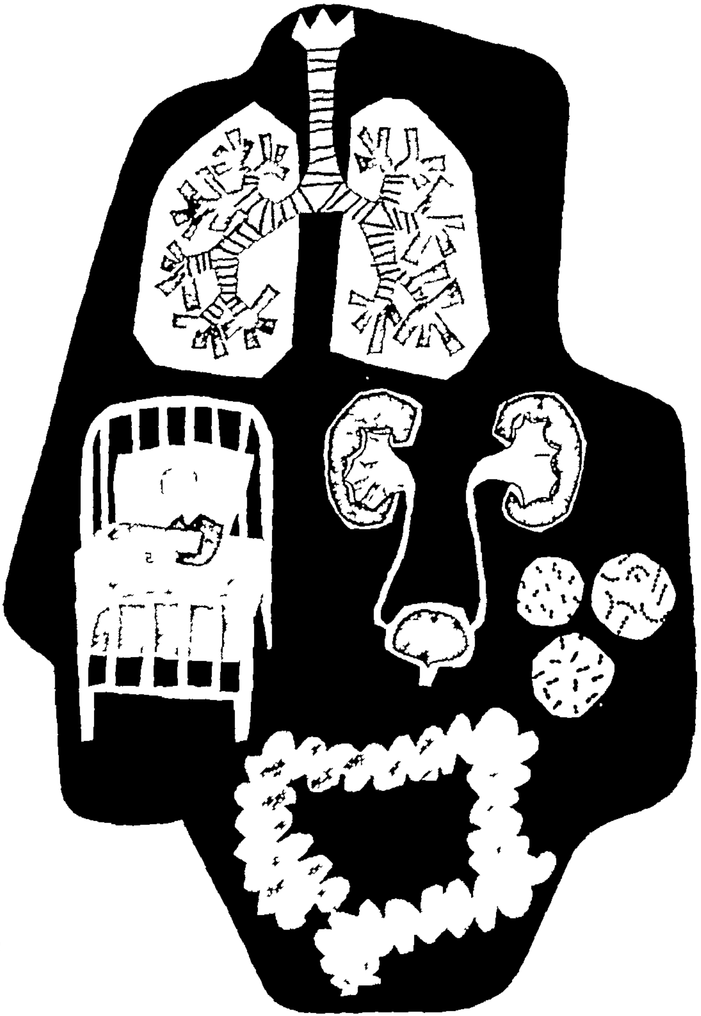

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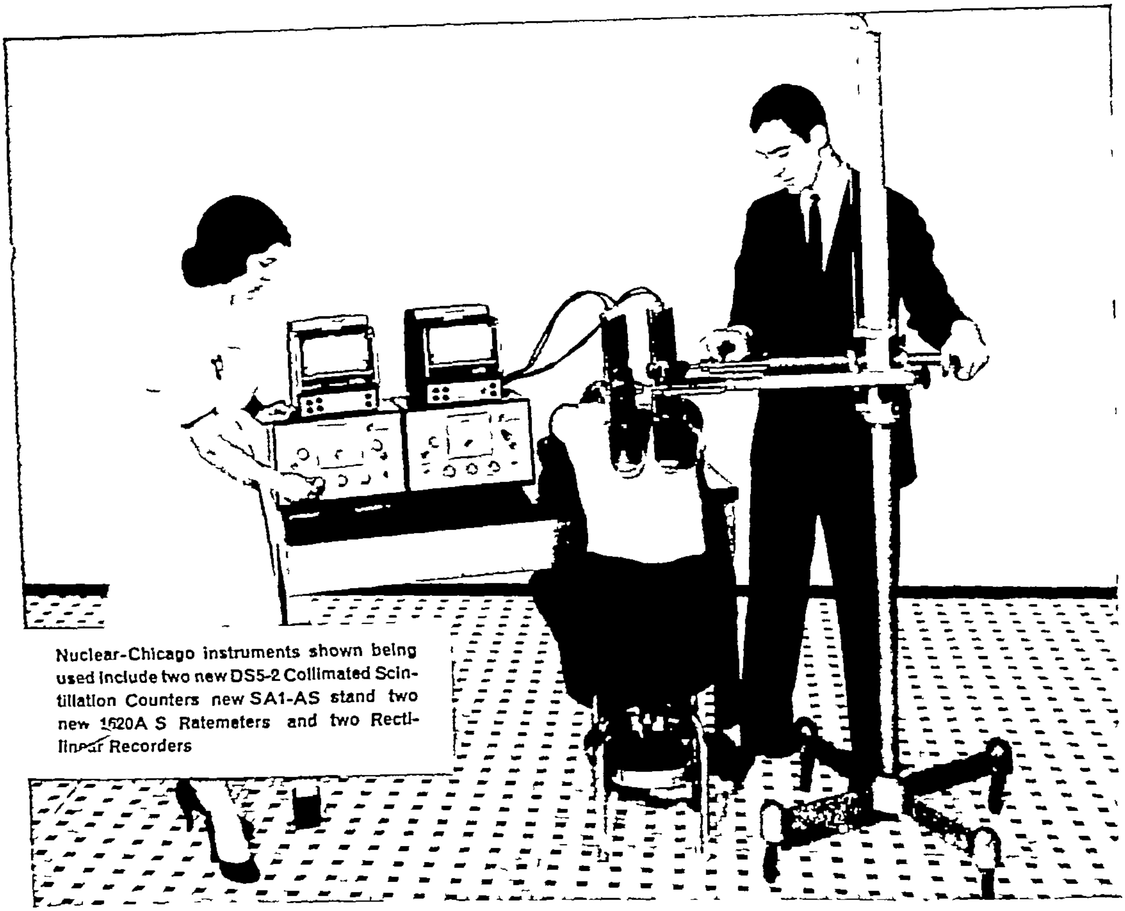

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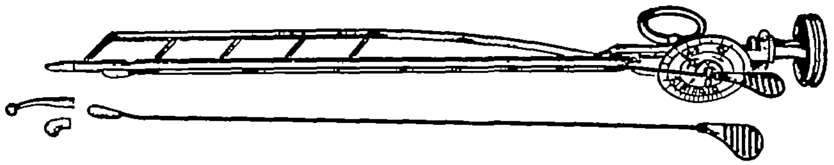

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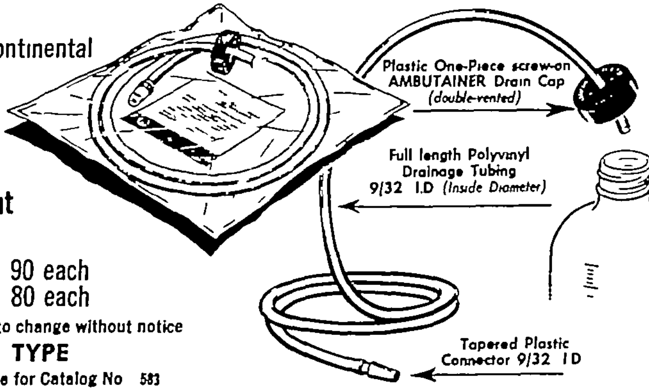
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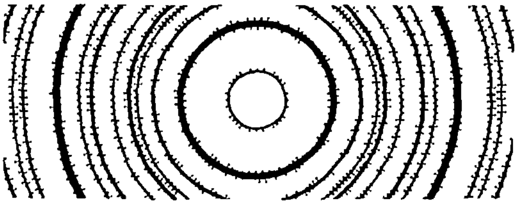

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Annual Meeting, American Urological Association, Hotel Roosevelt
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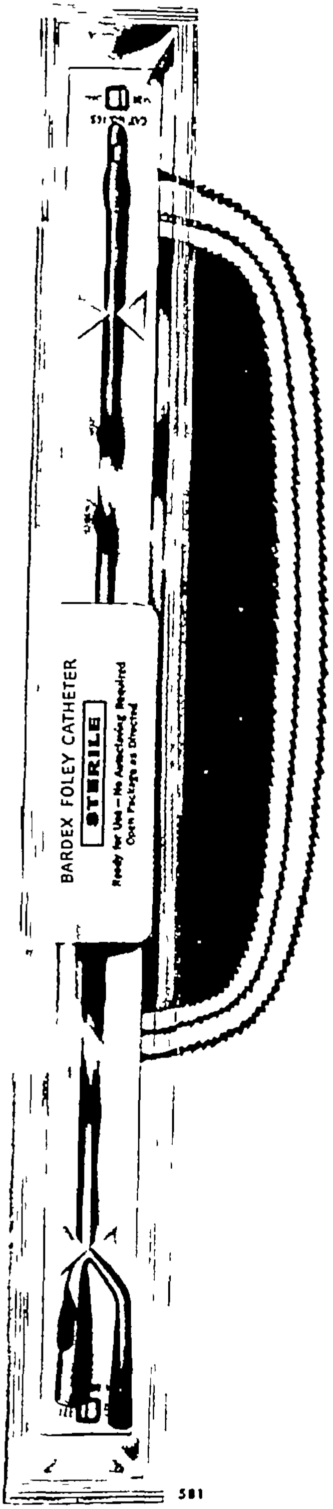

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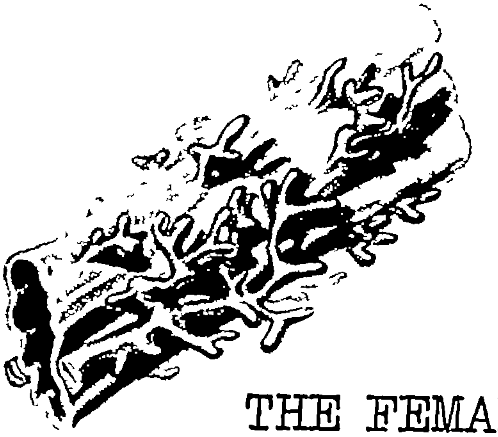

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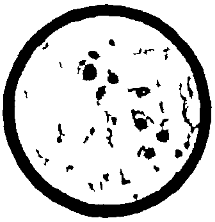

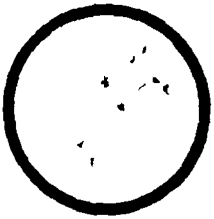

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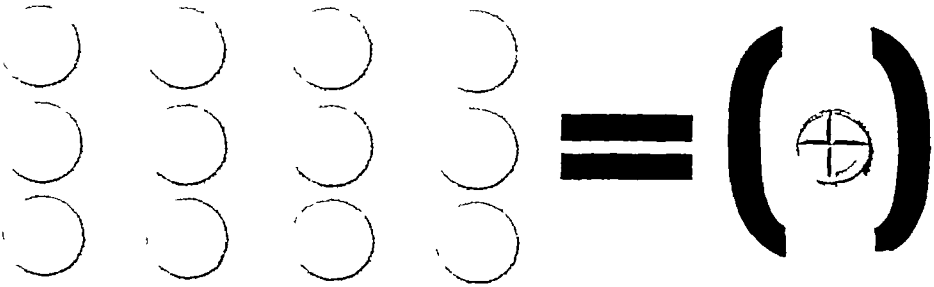

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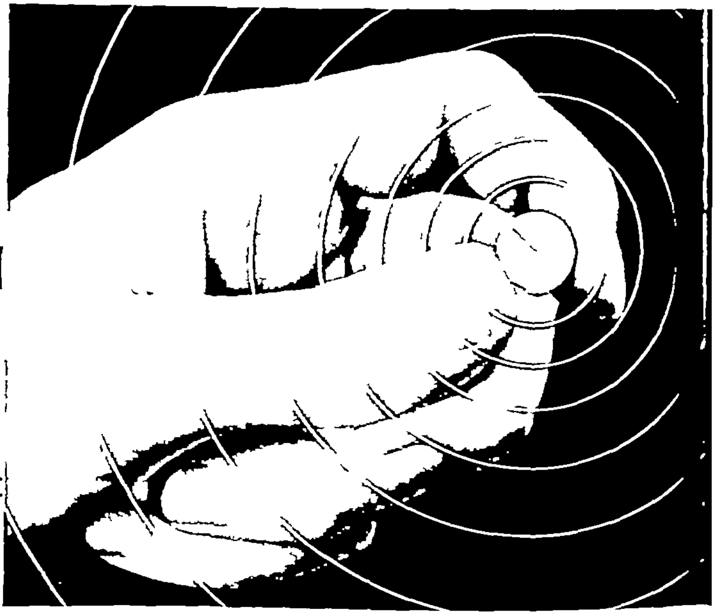

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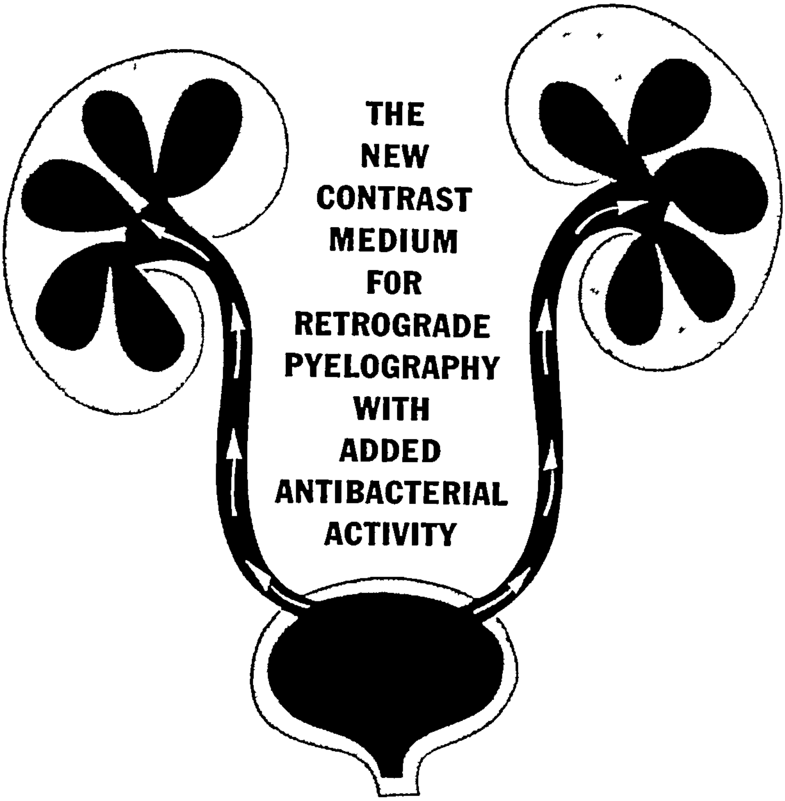

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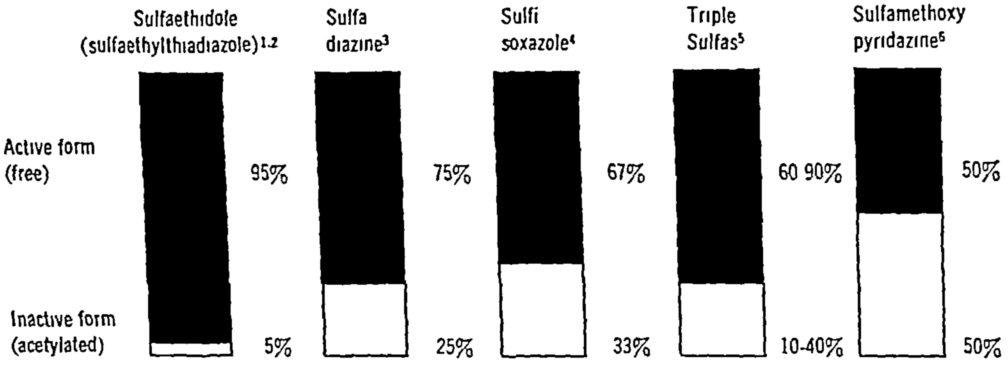

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2. Frisk, A R Sulfanilamide Derivatives Chemotherapeutic Evaluation of N^1-Substituted Sulfanilamides, Acta med scandinav Suppl *142* 1, 1943
3 Sophian R.H Piper D L, and Schneller G H The Sulfapyrimidines New York, A Colish, 1952, p 52
4 Goodman L S and Gilman, A The Pharmacological Basis of Therapeutics New York, The Macmillan Co, 1955, p 1316
5 *Ibid*, p 1289
6 Boger, W P Strickland, C S and Gylfe, J M Sulfamethoxypyridazine (Kynex) A New Long-Acting Sulfonamide, Antibiotic Med & Clin Therap *3* 378 (Nov) 1956

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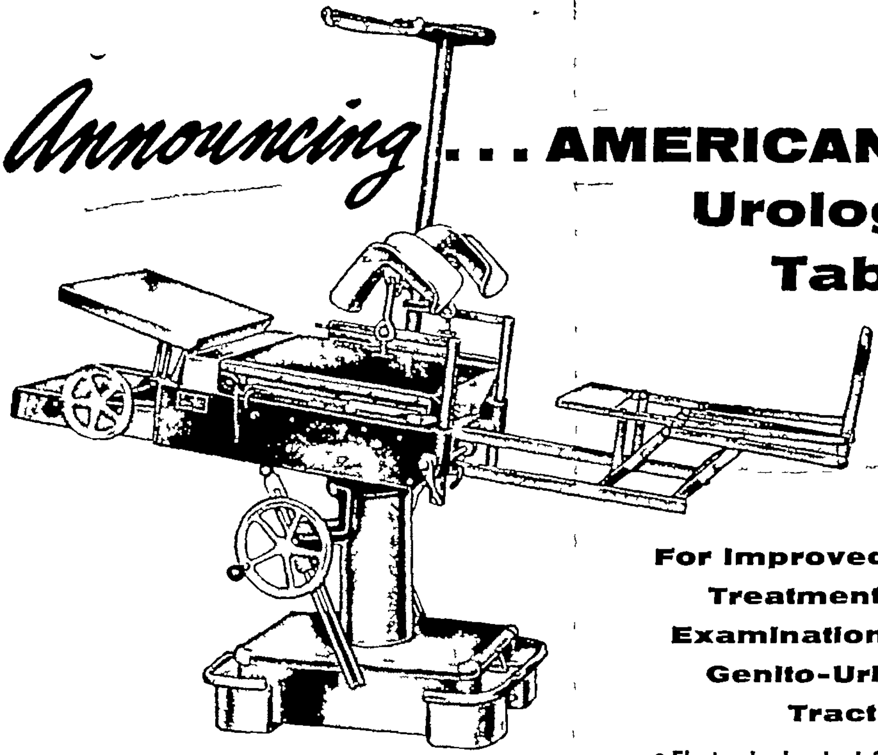

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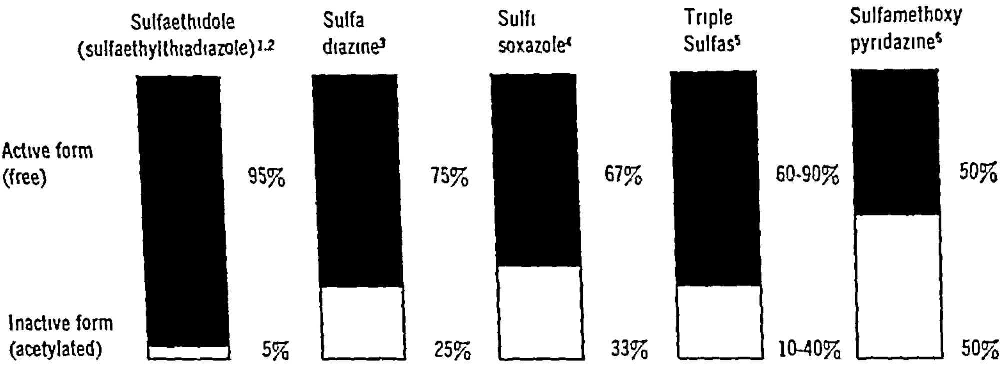
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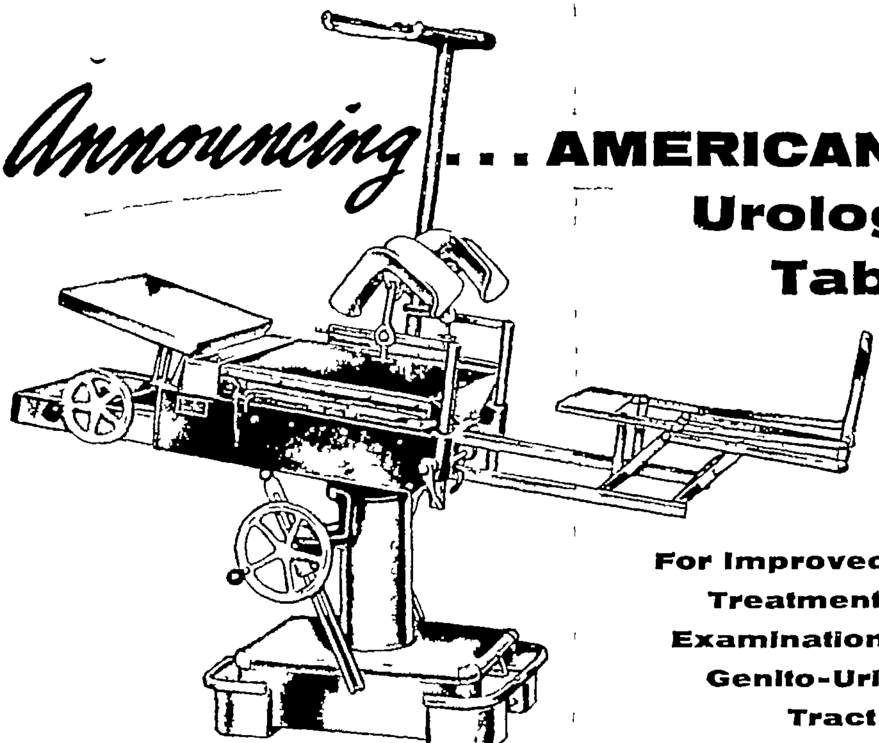

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1 Carlozzi M : Antibiotic Med & Clin Therapy 5:146 (Feb) 1958

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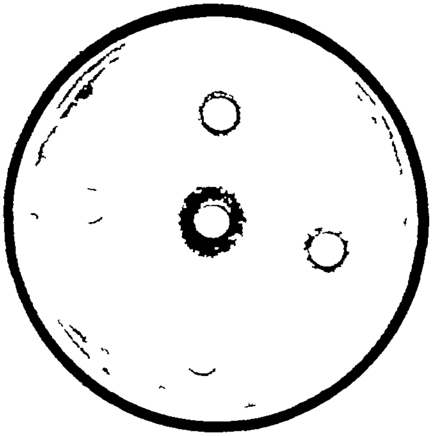

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of ☐ heart lung machines
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Effective against resistant organisms T B., Staph., Proteus, Yeasts and molds, Spores
Non toxic even without rinsing

REF Wolinsky E Smith M M and Steenken Wm. Jr Tuberculocidal Activity of Clorpactin. A new Chlorine Compound *Antibiotic Medicine* 1.382 384 July 1955

a product of the pharmaceutical division
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*Reg T M Contains Clorpactin® 2DC a stabilized organic hypochlorous acid derivative

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the obviously right combination of the original urinary tract analgesic and the classic triple sulfa for treatment of urinary tract infections

Relief of painful or uncomfortable symptoms quickly, prompt, efficient control of the infection, the only sulfa combination which provides Pyridium in the full therapeutic dose with only 1 tablet q. i. d.

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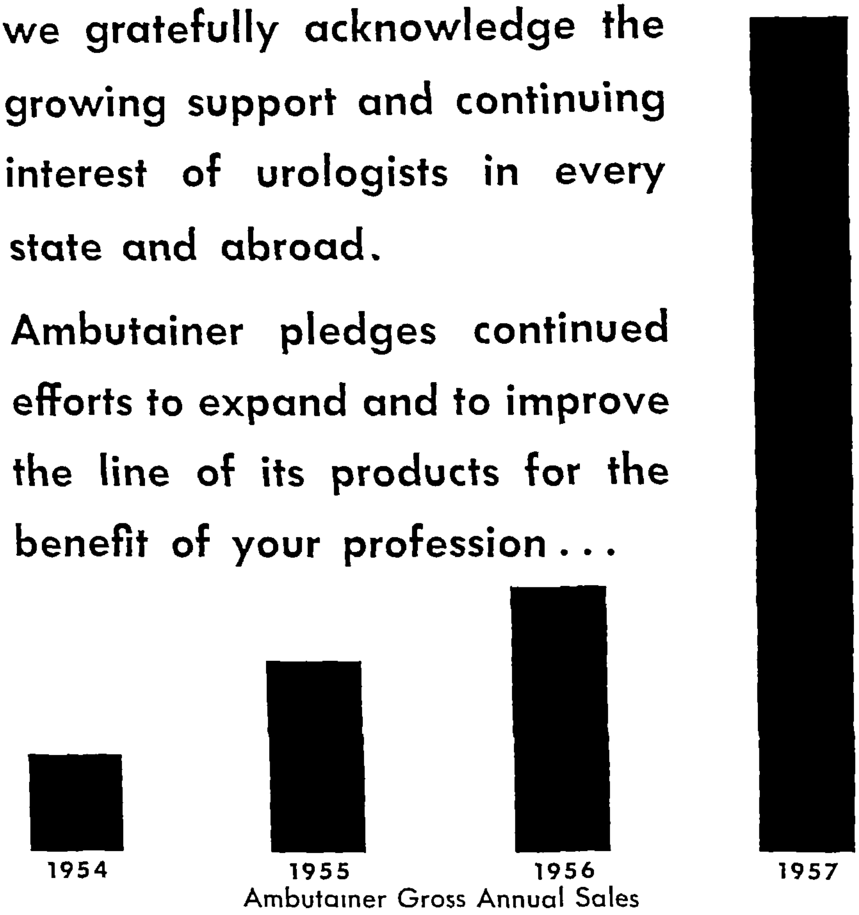
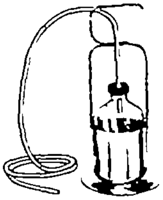
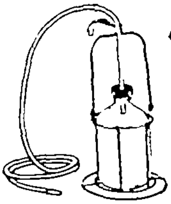
we gratefully acknowledge the growing support and continuing interest of urologists in every state and abroad.

Ambutainer pledges continued efforts to expand and to improve the line of its products for the benefit of your profession . . .




STANDARD MODEL AMBULANTERN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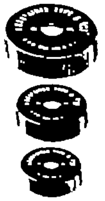
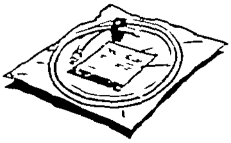
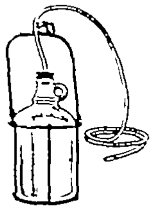

DRAIN CAPS


STERILE DRAINAGE SET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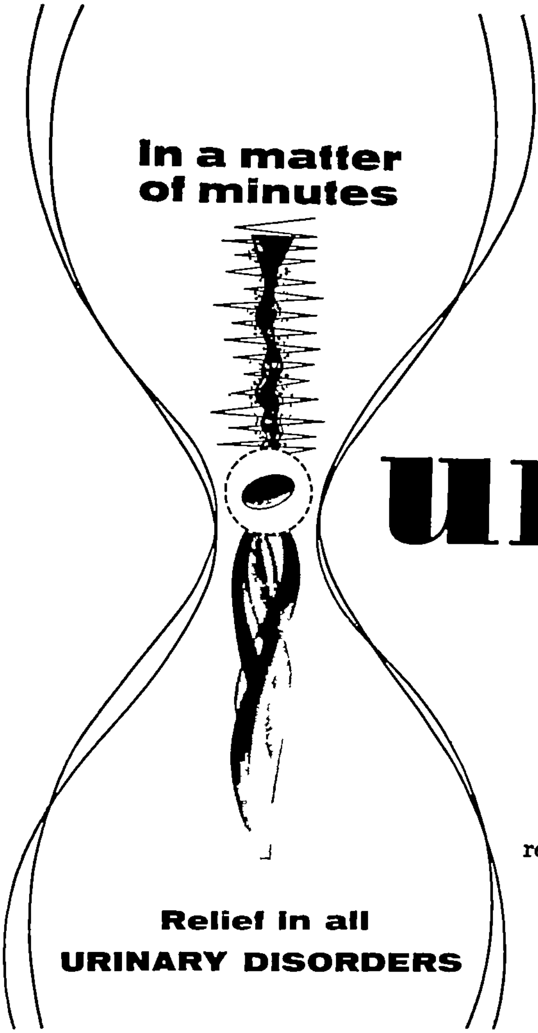

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Alleviates Pain
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ATTACKS THE CAUSE—In minutes, URISED attacks both primary causes of pain and dysfunction (1) smooth muscle spasm, (2) incidence of infection.

ALLEVIATES PAIN—Prompt antispasmodic action relaxes painful smooth muscle along the urinary tract, brings quick relief to the distressed patient

ARRESTS INFECTION—Rapid antibacterial action reduces irritation, even overcomes infections previously resistant to antibiotics and sulfonamides

Prescribe URISED with confidence to relieve frequency, burning, urgency, dysuria, promote rapid restoration of normal urinary function in all urinary affections of all age groups

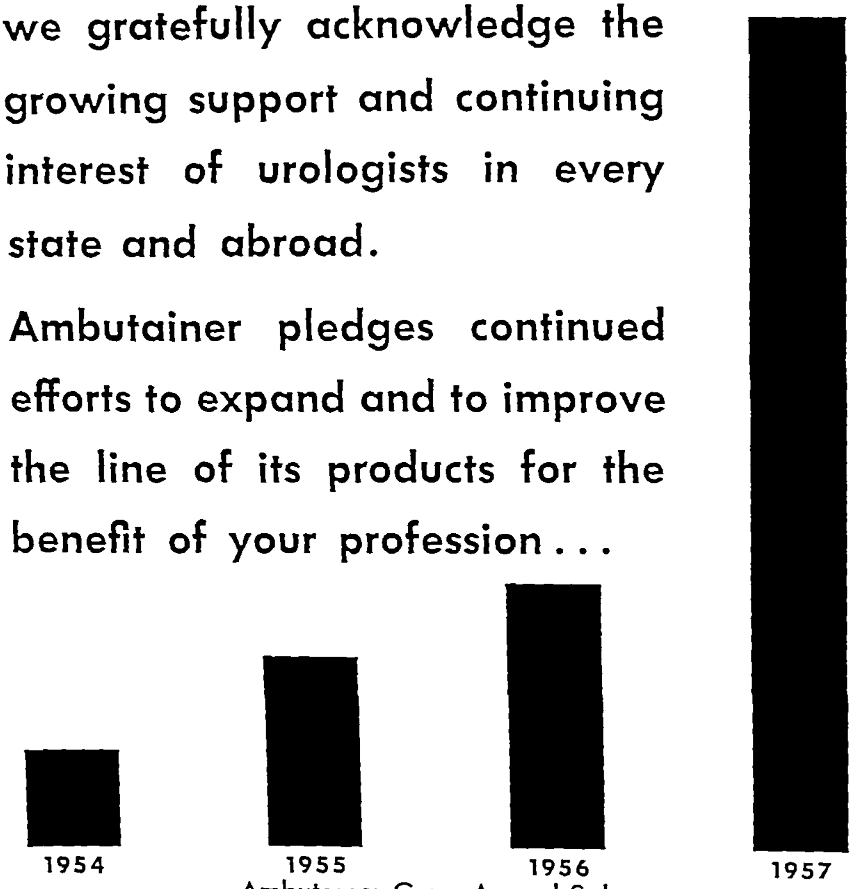
[1] Strauss, B., Clin Med Vol IV No 3 1957

CHICAGO PHARMACAL COMPANY
Chicago • San Francisco

As the Ambutainer Company starts its fifth year of service–

we gratefully acknowledge the growing support and continuing interest of urologists in every state and abroad.

Ambutainer pledges continued efforts to expand and to improve the line of its products for the benefit of your profession . . .



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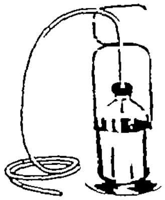

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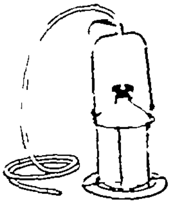

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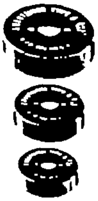
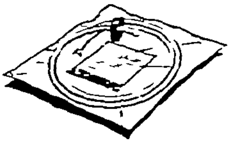
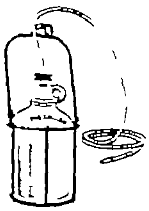
ADAPTER WITH DRAIN CAP



DRAIN CAPS



STERILE DRAINAGE SET



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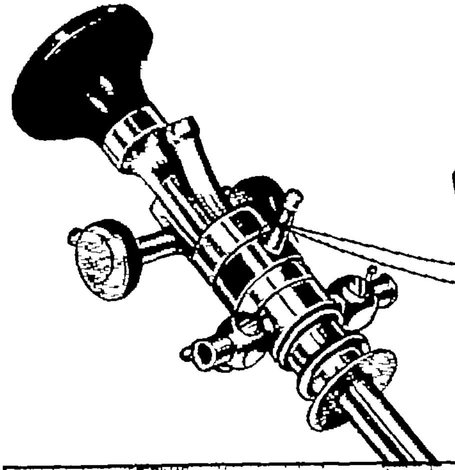

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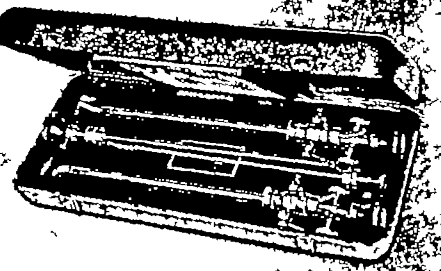

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*The already superb Fontar® optical system has been improved in this new 'BB' series of non rotating National cystoscopes The field of vision has been rendered brighter and eye-fatigue further reduced

**Now the telescopes and sheaths of the 'BB' cystoscopes and panendoscopes are completely interchangeable with like instruments of American manufacture

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Perhaps the most effective sulfonamide available today for urinary infections

Continuing studies show that Elkosin is one of the safest and most useful antibacterial agents known today For example

recently the results of sulfisomidine [Elkosin] therapy were evaluated in 55 additional patients with urinary tract infections 31 were cured 4 showed a good response With no attempt made to maintain an adequate daily fluid intake or alkalinization of the urine, no renal or hematopoietic toxicity occurred *

For systemic infections, too, Elkosin therapy is sound therapy

Rutenburg A. M. Ann New York Acad. Sc. 69:389 (Oct. 12) 1957

Elkosin®
(sulfisomidine CIBA)

SUPPLIED TABLETS 0.5 Gm (white double scored)
SYRUP (strawberry flavored) 0.25 Gm per 4-ml teaspoon

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CIBA
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*designed for
the surgeon
whose patients
can afford
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Personally Certified *

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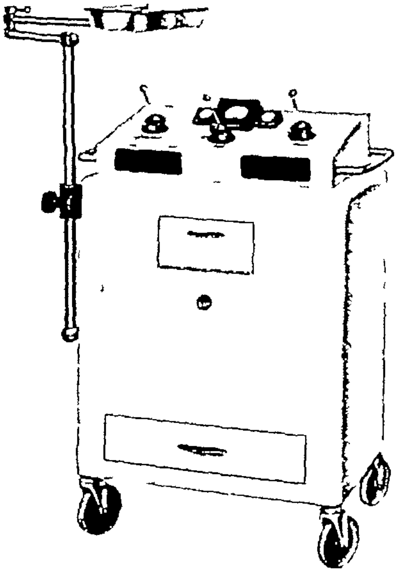

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Electrosurgical reprints and detailed specifications will be mailed to you on request. Please address your inquiry to

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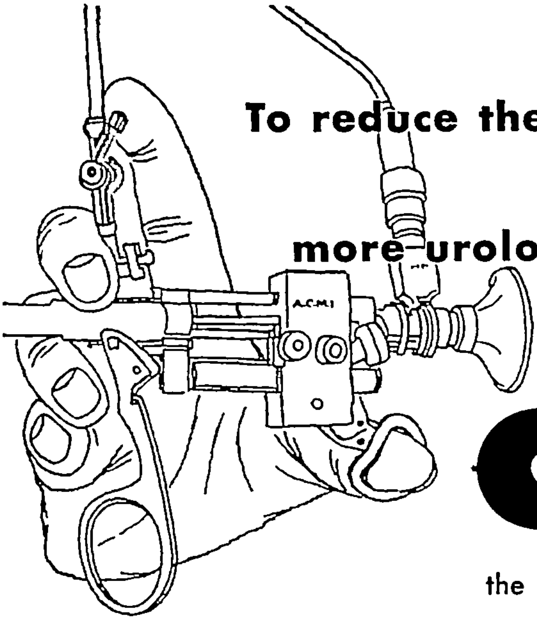

To reduce the risks in TUR surgery

more urologists are changing to

Cytal®

the nonhemolytic, isotonic irrigating fluid

because

Cytal is safer

- surgical mortality is reduced—when isotonic irrigating solutions were used instead of distilled water in 2492 consecutive transurethral prostatic resections, only 0 96% mortality was reported [1]
- hemolysis during resection is prevented
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- free of amino acids or nitrogen which can metabolize into toxic ammonia

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- tendency of blood to form free clots or fibrin masses in the bladder is reduced
- irrigation catheter does not become obstructed by clots

CYTAL* is available in sterile, pyrogen-free 1 liter Saftiflasks® ready for immediate dilution and use

*A concentrated solution of hexitols and parabens

1 Creevy C D Surgery *39* 180 1956

2. Schulte R. L. Hammer H J and Reynolds, L R J Urology *71* 656 1954

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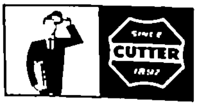

CUTTER LABORATORIES Berkeley, California

PROSTATIC CARCINOMA

higher survival rates even in advanced cases[13]

TACE

(chlorotrianisene)

three-year survival rates range from 70-80%[1,2]

TACE is effective where other estrogens fail[1,5] even in advanced cases Because TACE is stored in body fat, it is liberated gradually and does not activate the adrenal or pituitary gland[2] TACE is better tolerated over prolonged periods[6] no edema, no nausea or vomiting[2] feminization is minimal[1,6] There is, however, a gratifying reversal of the pathologic picture relief of pain, regression of lesions, weight gain[2]

References:

1 O Conor V J and Sokol J K Quart Bull Northwest U M School 26 161 1952 2. Carroll G and Brennan R V J A M A 157 581 1955 3 Smith P G et al J Urol 65 886 1951 4 Politano V A and Alyea E P TACE Symposium 1952 5 Headstream J W Trans South Central Sec Am Urol Assoc 1954 6 Mortensen H M J Australia 1 728 1953

Dosage 1-2 capsules daily

TRADEMARK TACE®

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SINCE 1828

THE WM S MERRELL COMPANY
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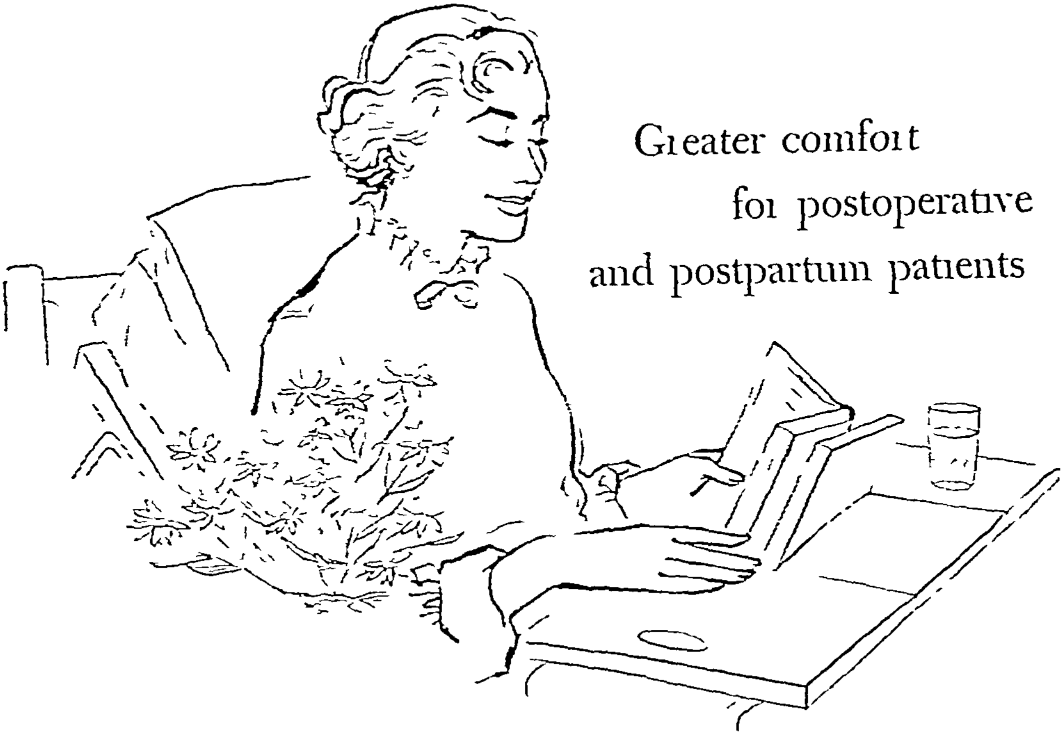
Another Exclusive Product of Original Merrell Research



Greater comfort
for postoperative
and postpartum patients

*abdominal distention and urinary retention
can often be prevented or promptly relieved
—with less need for uncomfortable enemas and catheters*

Urecholine®
Chloride
(Bethanechol Chloride)

Urecholine helps restore normal function after surgery and childbirth by increasing the muscular tone of the gastrointestinal and urinary tracts. Postoperative "gas" pains can frequently be prevented or promptly relieved—with less need for uncomfortable enemas, intubation and suction apparatus. Micturition is facilitated—without the discomfort and risk of infection inherent in catheterization.

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Supplied: 5 mg. and 10 mg. tablets, bottles of 100. 1-cc. ampuls containing 5 mg.

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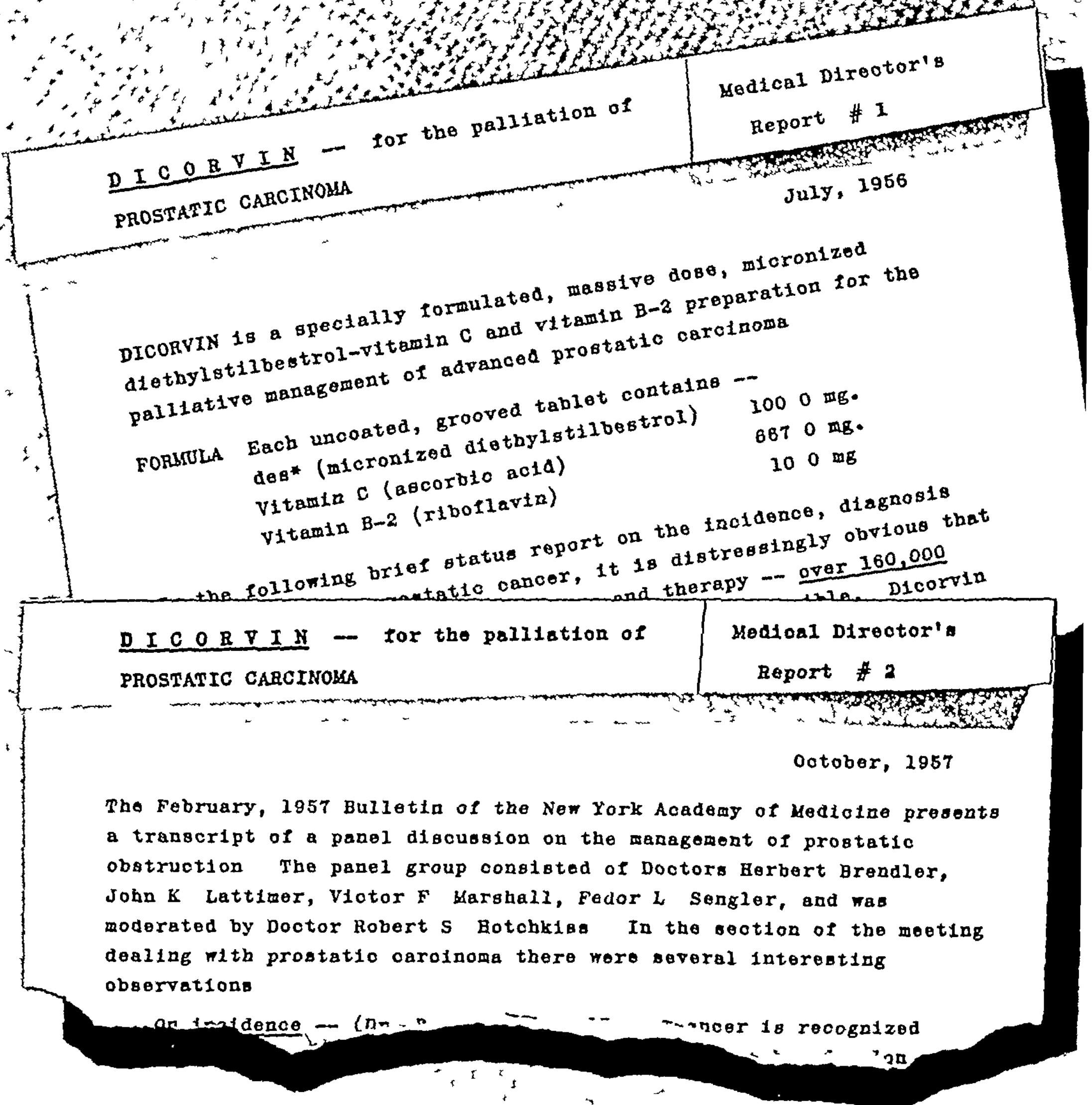


D I C O R V I N — for the palliation of
PROSTATIC CARCINOMA

Medical Director's
Report # 1

July, 1956

DICORVIN is a specially formulated, massive dose, micronized diethylstilbestrol-vitamin C and vitamin B-2 preparation for the palliative management of advanced prostatic carcinoma

FORMULA	Each uncoated, grooved tablet contains --	
	des* (micronized diethylstilbestrol)	100 0 mg.
	Vitamin C (ascorbic acid)	667 0 mg.
	Vitamin B-2 (riboflavin)	10 0 mg

the following brief status report on the incidence, diagnosis ...ostatic cancer, it is distressingly obvious that ...and therapy -- over 160,000 ...ible. Dicorvin

---

D I C O R V I N — for the palliation of
PROSTATIC CARCINOMA

Medical Director's
Report # 2

October, 1957

The February, 1957 Bulletin of the New York Academy of Medicine presents a transcript of a panel discussion on the management of prostatic obstruction The panel group consisted of Doctors Herbert Brendler, John K Lattimer, Victor F Marshall, Fedor L Sengler, and was moderated by Doctor Robert S Hotchkiss In the section of the meeting dealing with prostatic carcinoma there were several interesting observations

On incidence -- ...cancer is recognized

...deal with prostatic cancer and

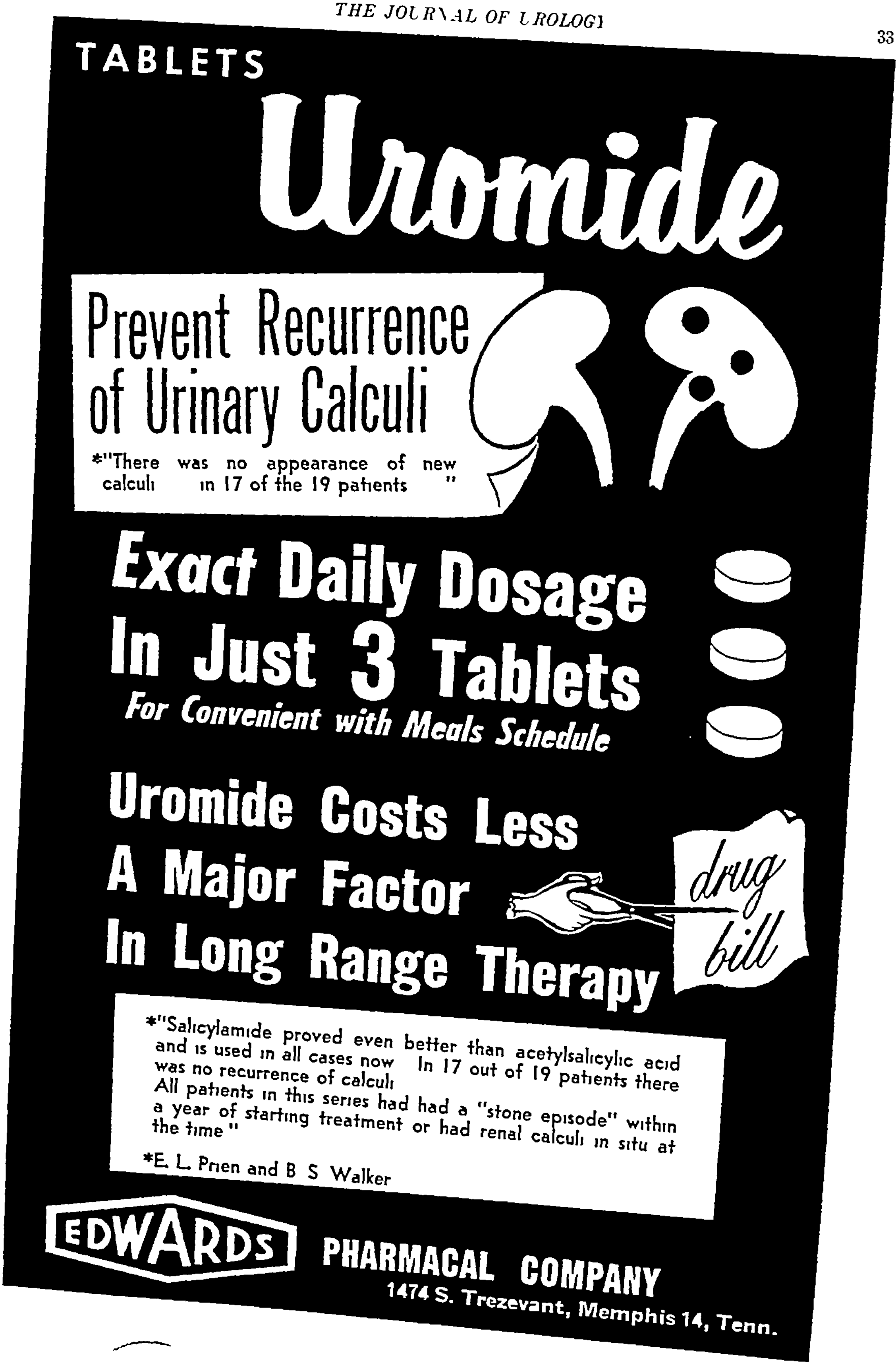
DICORVIN™ TABLETS

a formulation that can mean a fuller life for many of your patients

Dose 1 3 tablets daily Supply Bottles of 50, 100 500 – on prescription only

A&O

Should you like a copy of



TABLETS

Uromide

Prevent Recurrence of Urinary Calculi

*"There was no appearance of new calculi in 17 of the 19 patients "

Exact Daily Dosage In Just 3 Tablets

For Convenient with Meals Schedule

Uromide Costs Less A Major Factor In Long Range Therapy

*"Salicylamide proved even better than acetylsalicylic acid and is used in all cases now In 17 out of 19 patients there was no recurrence of calculi All patients in this series had had a "stone episode" within a year of starting treatment or had renal calculi in situ at the time "

*E. L. Prien and B S Walker

EDWARDS PHARMACAL COMPANY
1474 S. Trezevant, Memphis 14, Tenn.

In urinary-tract infections

SUSPENSION **TABLETS**

SULFOSE®

Triple Sulfonamides Wyeth
(Trisulfapyrimidines Sulfadiazine
Sulfamerazine, Sulfamethazine)

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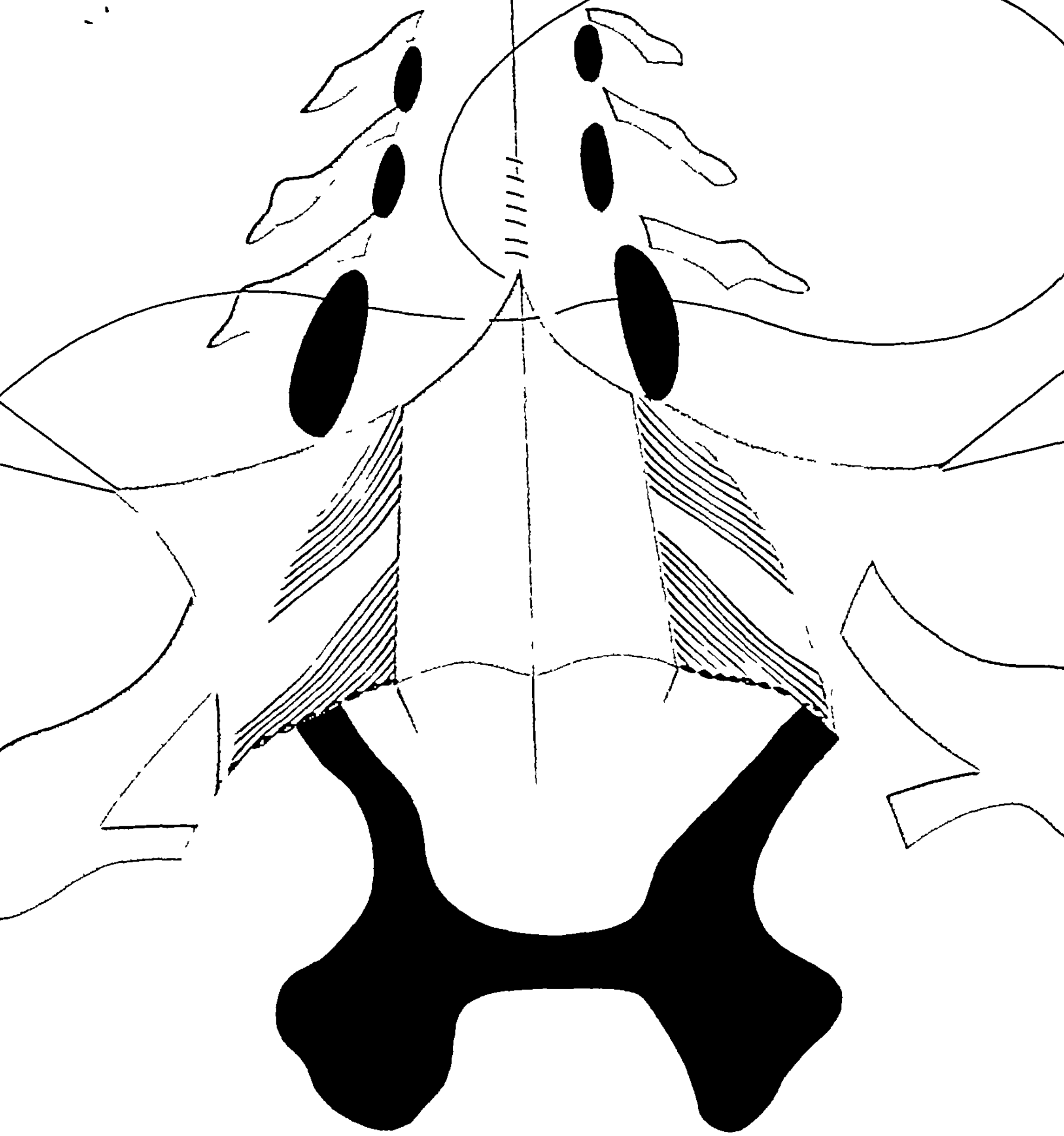

setting new standards

ETHICON®

sutures

In urinary-tract infections

SUSPENSION TABLETS

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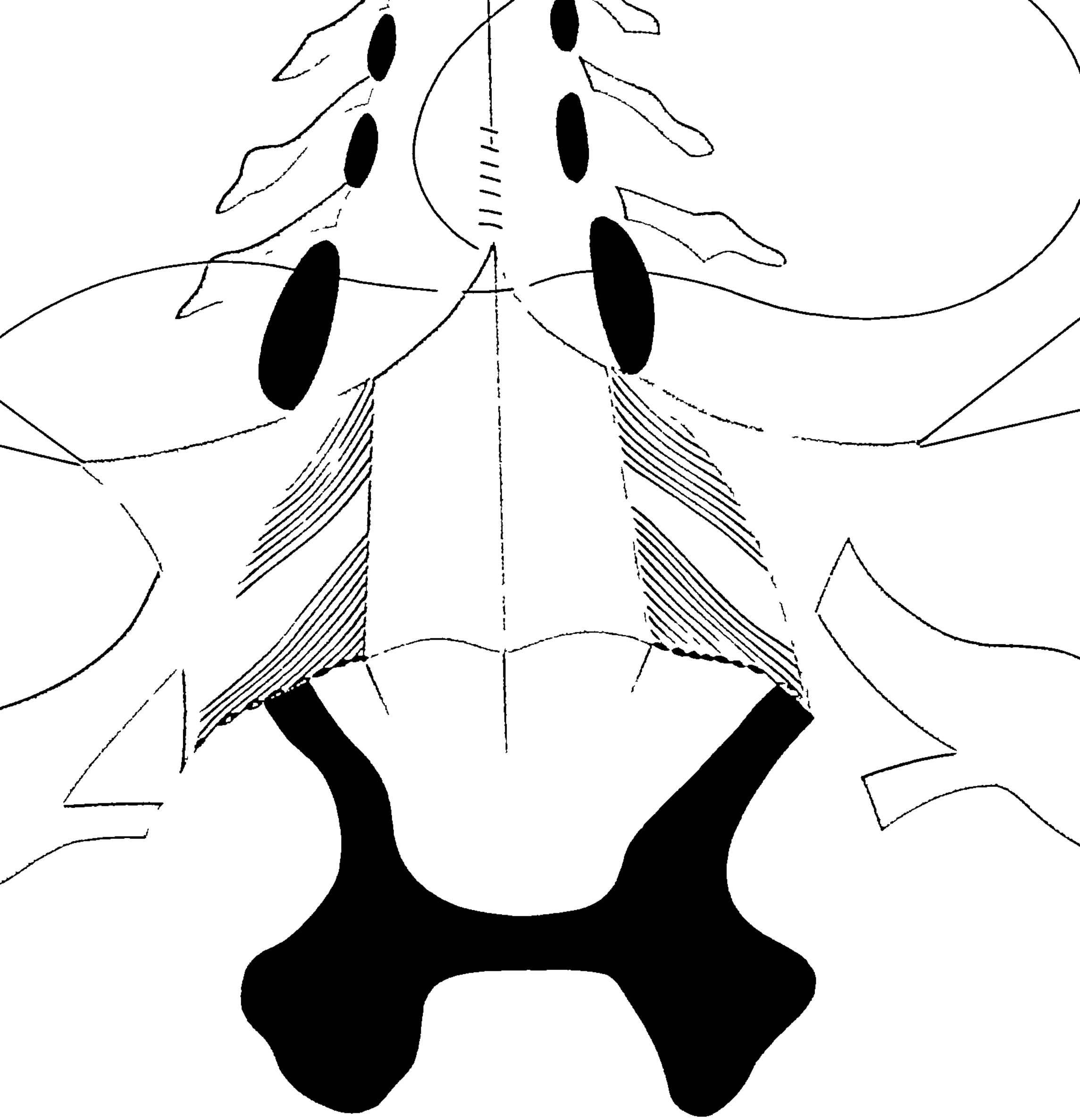

setting new standards

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sutures

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seamless needles

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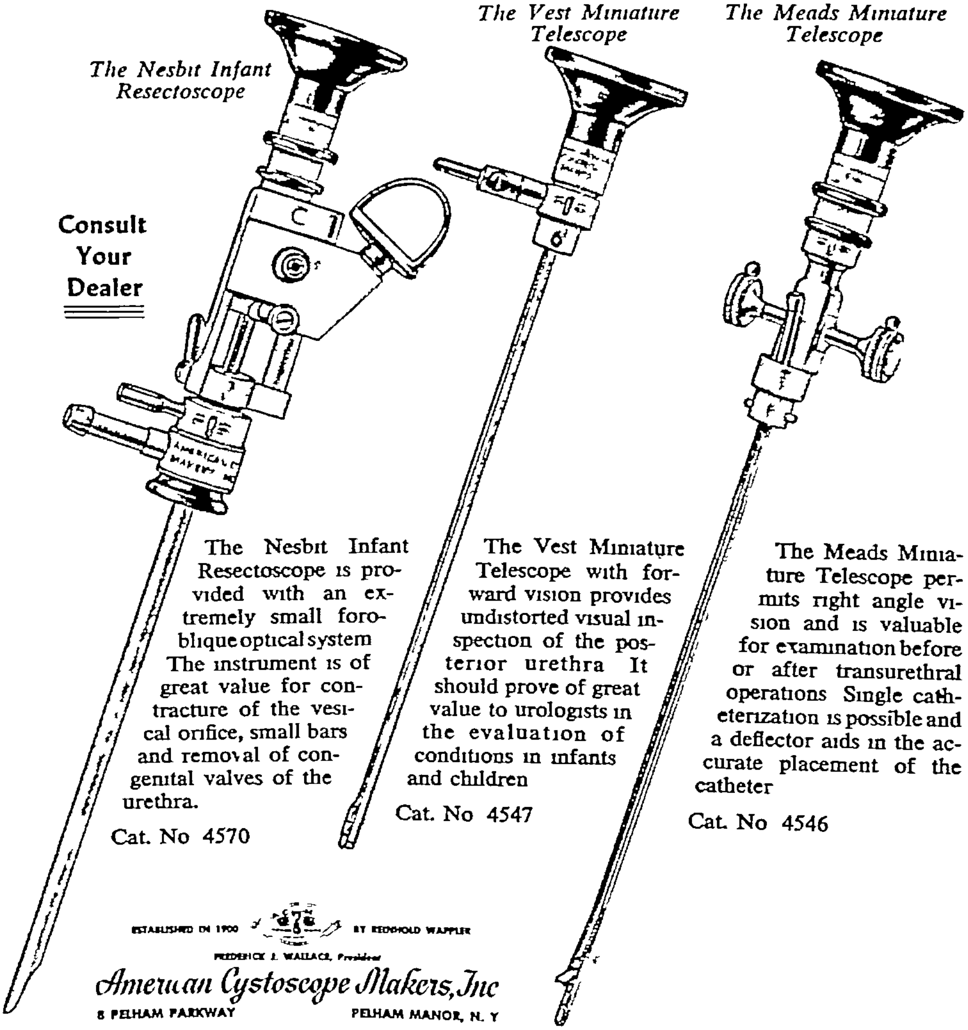
The
NESBIT INFANT RESECTOSCOPE
with
ACCESSORY VEST MINIATURE FORWARD VISION and MEADS RIGHT ANGLE TELESCOPE

Urologists will recognize the value of these miniature telescopes for use in transurethral procedures on infants and children They provide clear, bright images and make possible visualization of the bladder neck and urethra not obtainable with the foroblique telescope

These miniature telescopes are used with the Nesbit infant resectoscope sheath and they should prove to be worthwhile additions to the urologist's instrumentarium

NOTE *The accessory telescopes may also be used with the McCarthy Infant Electrotome*



The Nesbit Infant Resectoscope

The Vest Miniature Telescope

The Meads Miniature Telescope

Consult Your Dealer

The Nesbit Infant Resectoscope is provided with an extremely small foroblique optical system The instrument is of great value for contracture of the vesical orifice, small bars and removal of congenital valves of the urethra.

Cat. No 4570

The Vest Miniature Telescope with forward vision provides undistorted visual inspection of the posterior urethra It should prove of great value to urologists in the evaluation of conditions in infants and children

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The Meads Miniature Telescope permits right angle vision and is valuable for examination before or after transurethral operations Single catheterization is possible and a deflector aids in the accurate placement of the catheter

Cat. No 4546

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FREDERICK J. WALLACE, President
American Cystoscope Makers, Inc
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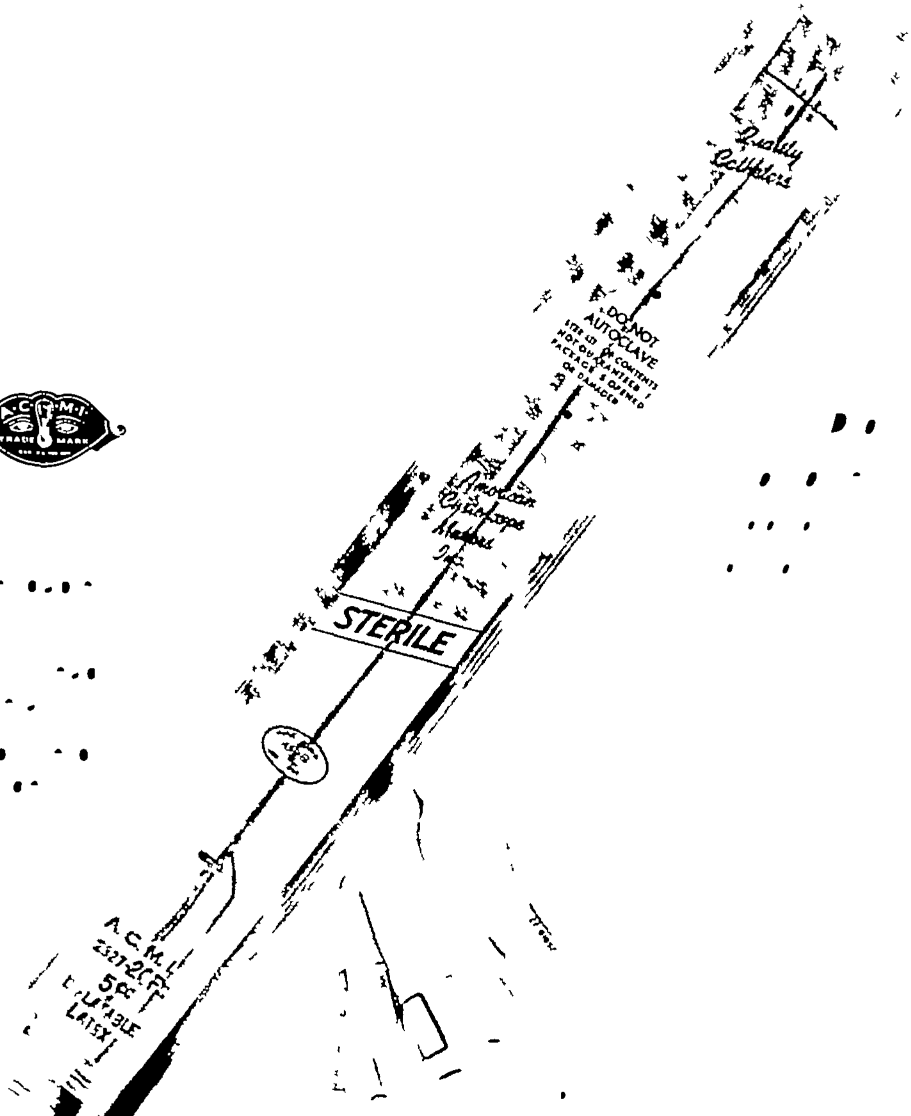
A·C·M·I· TRADE MARK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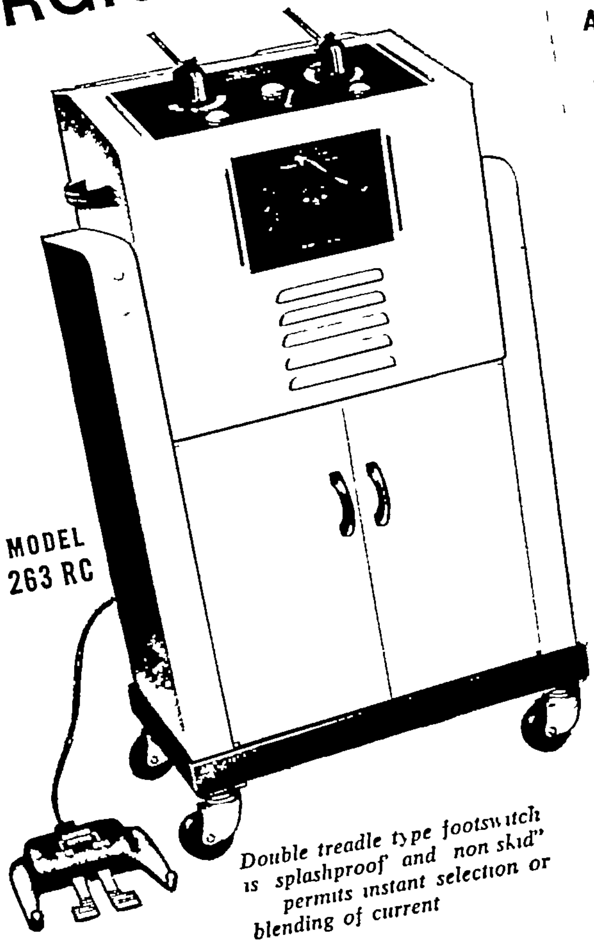

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ABUNDANT POWER OUTPUT— to sever any tissue, and for rapid massive coagulation

TWO SEPARATE CIRCUITS— vacuum tube circuit for cutting current, spark-gap circuit for coagulating current

SIMPLICITY OF OPERATION— single "stepless" control for each circuit permits easy, exact regulation of current intensity

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COLOR INDICATOR LIGHTS —show when power line switch is on and which type of current is in use

SPECIAL CONTROL HANDLES — removable for sterilization

INCLUDED WITH EACH UNIT—inlet cable, footswitch indifferent plate with conducting cord, three active conducting cords, three chuck handles, set of eight surgical electrodes

See this precision-engineered unit at your dealer's or write for complete information

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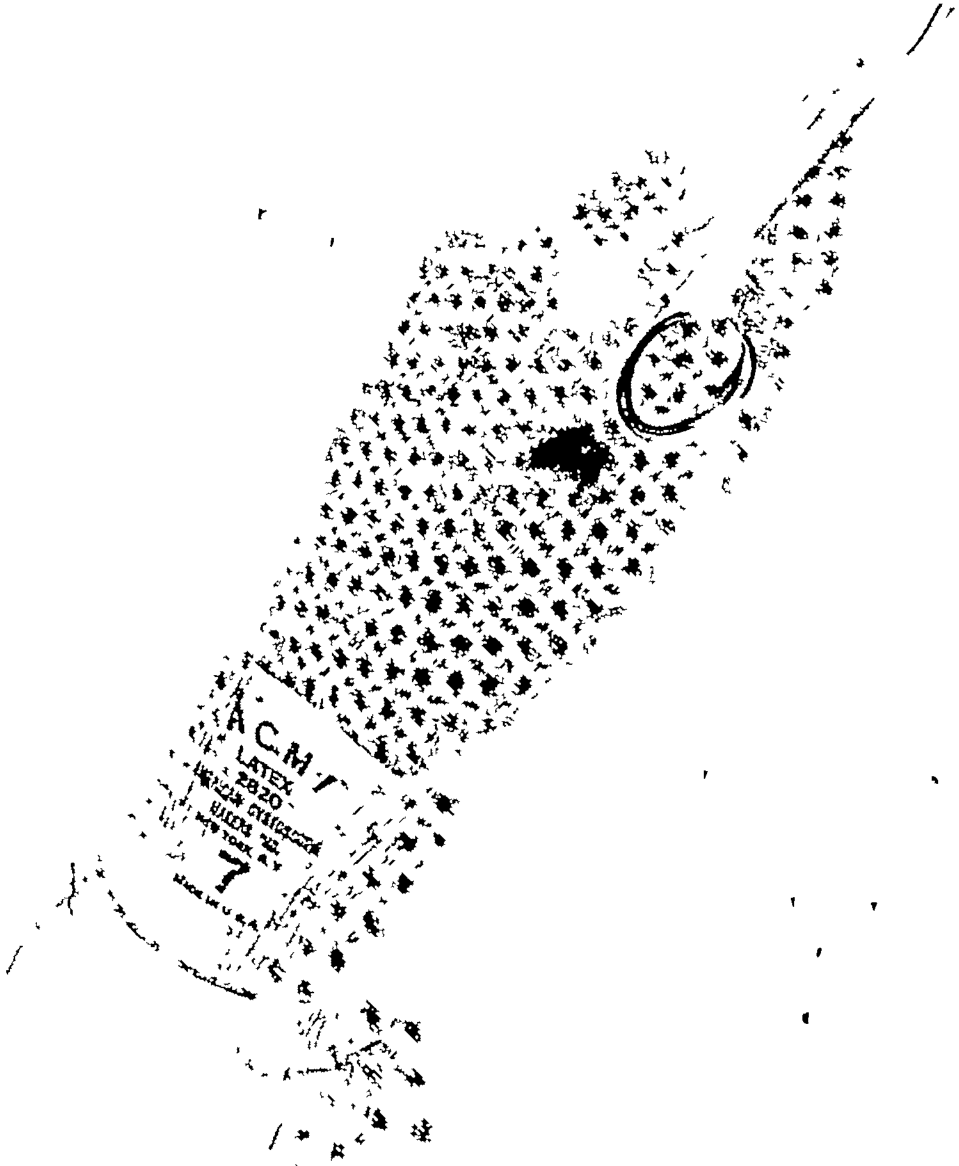
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THE JOURNAL OF UROLOGY
Vol 79 No. 4 April 1958
Printed in U.S.A.

PANEL DISCUSSION UNDERGRADUATE TRAINING IN UROLOGY

DR CHARLES C HIGGINS* (moderator) Mr Chairman members and guests May I present to you the members of the panel Dr O W Hyman dean of the University of Tennessee School of Medicine Dr George M Piersol, dean of the Graduate School of Medicine University of Pennsylvania Dr Edgar Burns, professor of urology Tulane University Due to illness Dr George F Cahill of the Department of Urology, Columbia University will be unable to participate in the panel this morning Dr Grayson Carroll associate professor of urology, St Louis University has kindly agreed to substitute for him

In view of the enthusiasm expressed by members of this society last year following the presentation by Dr Ormond Culp of his committee's survey of ' The Present Status of Undergraduate Urologic Teaching '† the program committee decided a consideration of this subject would be of general interest this year Today various phases of this subject will be presented by members of the panel including a brief consideration of graduate teaching in urology

The diversity of opinion which prevails on the undergraduate teaching of urology is not confined to this branch of science, but encompasses education in general This diversity is a reflection of the social, economic and political changes that are encouraged and fostered in a democracy Some of the influences and changes may be briefly considered

As Dr Robert A Moore has stated Freedom from disease is one of our basic freedoms and this freedom cannot be attained or maintained without the product of medical schools i e physicians ' Since 1910 with the reorganization of medical education resulting from the Flexner report financial support of medical schools has been sponsored by private philanthropy, industrial contributions, and federal and state assistance Dr Moore has emphasized the public interest in medical education and research Through the support of the public foundations and federal government grants, it is estimated that two hundred million dollars is available each year for these purposes

In a short span of years corporate business has become a major source of philanthropic funds assigned for higher education It is estimated that in 1956 industrial grants to higher education for all purposes approximated $100 000,000 This is in contrast to $40,000,000 appropriated in 1950 The Ford Fund for the Advancement of Education recently announced that it is investing one million dollars in a project aimed at turning the nation's public school teachers into television educators This increase in industrial grants signifies that business management is cognizant of the acute financial distress of our colleges and uni-

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Presented at annual meeting of American Urological Association Pittsburgh Pa, May 6-9 1957

Reprints of the panel discussion may be obtained from the American Urological Association 1120 N Charles St Baltimore 1 Md

* *Note by editor* Head Department of Urology The Cleveland Clinic Foundation Cleveland Ohio

† The present status of undergraduate urologic training report of the committee to study status of urology in medical school J Urol 76 309-322 1956 (Reprints of the report may be obtained from the American Urological Association 1120 N Charles St., Baltimore 1 Md.)

versities. Such generosity indicates corporations are accepting their responsibilities and obligations.

The threat of increased federal subsidy cannot be ignored or minimized. Increased appropriations by the federal government will be followed by the government's adopting a dictatorial role in medical education. This is attested by the policy advocated and later assumed by the government in vocational education. In the brochure published by the United States Department of Education on vocational training it is stated unequivocally that federal support will be granted only to those vocational educational programs that are approved in Washington. Medical education must be maintained free from the incubus of governmental interference and the encumbrance of political domination. This is of especial significance if academic freedom is to be maintained in our medical institutions.

The financial burden assumed by the student attending medical school constitutes a major problem today in the throes of inflation. In fact it poses a problem for any ambitious individual desiring higher education. It is estimated that the cost of attending college has more than doubled since 1940. The tuitions of many educational institutions, i.e. colleges and universities, range from $800 to $1200 each year. Even with the tuition fee at this level it is estimated it pays for less than 50 per cent of the cost to the college for educating a student. It has been stated that tuition fees cannot be increased much more, and still retain the democratic concept that has made higher education so unique in this country.

Graduate training programs acceptable to the specialty boards foster further financial obligations. If worthy and qualified students desiring to pursue a career of alleviating human suffering are deprived of this opportunity because of financial problems, our democratic ideals will be shattered.

In recent years a rebirth of interest in the humanities has become evident, not only in the education of physicians but most professional groups. It is quite evident that more students desire to devote additional time to the humanities. This trend has been recognized and is to be incorporated in the medical educational program contemplated by the Johns Hopkins School of Medicine, which I shall briefly mention in a few moments. Physicians with a broad general grounding in the humanities and the liberal arts strengthened by adequate medical training are essential today to elevate the standards of medicine and surgery in this country.

Recently, a revised program of medical education was announced by the Johns Hopkins School of Medicine. The objectives are to graduate more doctors in less time and to broaden the scope of their education. These may be enumerated as follows:

1) To shorten the period of formal education required to train doctors without sacrificing the quality of their training.

2) To overcome the "artificial barrier" which now exists between the medical sciences and the liberal arts. This will be accomplished by having the medical students continue studies in the humanities and social sciences while attending medical school.

3) To lengthen the academic year so that instead of having 32 weeks of required class work followed by 4 months of summer vacation students in the proposed program will attend classes for 40 weeks of each year In the final year as hospital interns they will be enrolled for 12 months except for 2 weeks vacation

This procedure is in effect in certain European countries and has proven to be a very satisfactory arrangement Thus the proposed plan to be initiated at Johns Hopkins permits the combined medical school-internship program to be shortened by one year If such a program can be offered without reducing the quality of medical education it will permit a reduction in the economic stress to the student and at the same time promote a professional training in which medicine is related in meaningful terms to the basic liberal tradition of learning

The world is plagued with social, economic and political problems The medical profession is not immune to playing an important role in their solution Without broad basic learning in the humanities and liberal arts their task is rendered more difficult Certainly we may assert our leadership effectively by maintaining high ideals and maintaining broad standards of excellence acquired by such an educational program

I have spoken this morning in generalities while the members of the panel will consider specific problems in undergraduate education

DR BURNS The primary function of the medical school is to train personnel to serve the health needs of the public and the curriculum should be designed to fulfill that purpose The quantity and complexity of medical information with the progressive increase in medical knowledge create a demand for more and more new courses and therefore interval revisions of the curriculum The basic structure however must remain the same

In the undergraduate course the faculty should not be concerned about the student s future scientific interest but all efforts should be blended toward helping him acquire habits of study and a capacity for independent thinking that will enable him to continue his medical education in any direction he may choose after he leaves the medical school

The number of students who will pursue an academic career after graduation go into general practice specialize or enter some other field of medical activity will vary from one class to another Regardless of the student s future course orientation as to basic physiologic functions of the various systems recognition and management of commonly encountered diseases and effective means of preventive medicine are important to all

These are important to the general practitioner if he is to render the best service to his community They are equally important to those who will pursue other courses of scientific endeavor as without such experience they would not know what phase of medicine might absorb their interests or for which their capabilities might be best suited Probably every teacher sincerely hopes that he will present his subject in such an interesting manner that a significant number of students will continue the same course of study after graduation

A rather widespread feeling that urology was being de-emphasized in a number versities Such generosity indicates corporations are accepting their responsibilities and obligations

The threat of increased federal subsidy cannot be ignored or minimized Increased appropriations by the federal government will be followed by the government's adopting a dictatorial role in medical education This is attested by the policy advocated and later assumed by the government in vocational education In the brochure published by the United States Department of Education on vocational training it is stated unequivocally that federal support will be granted only to those vocational educational programs that are approved in Washington Medical education must be maintained free from the incubus of governmental interference and the encumbrance of political domination This is of especial significance if academic freedom is to be maintained in our medical institutions

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others, however, whose qualifications are such that they would be desirable students in any school they might select A particular school is undoubtedly chosen on the basis of evaluation of the various departments, the qualifications of the faculty, the professional accomplishments of its alumni as well as the school's national rating A good student's progress is enhanced by a strong faculty, and many good physicians have been developed from poor students by intelligent leadership

Time allotted for the course The curriculum must provide enough time for adequate presentation of the course It is important, however, to conserve time in order to avoid adding to the burden of the already overcrowded schedule that exists in every medical school It should be possible to accomplish this without sacrifice of any of the essentials of the course Much time can be saved by concentration on the common problems that the student will encounter in practice and avoidance of wasting time in exploring the differential diagnosis of obscure lesions that he may never see

Urology, a department or division Whether or not urology is a division of general surgery or has an independent status is probably important only from standpoint of personalities Our department at Tulane University is a division of the Department of General Surgery, and our experience over a number of years has been that this arrangement has a number of recognizable advantages We would not elect to change that status

The urologic curriculum The report of the Culp Committee showed tremendous variation in urologic teaching from one school to another The general pattern in the average curriculum, however, includes urologic physical diagnosis, formal lectures, teaching in the outpatient department, bedside teaching and student clerkships on the inpatient service

The year that the student is introduced to urology is, in our opinion, of more than ordinary importance For a number of years, urology at Tulane University has been a part of a block system given during a fixed period of the senior year We have had ample opportunity to evaluate urologic teaching at this level and believe that it would be more effective to introduce urology to the student earlier by appropriate integration of the course with the other departments We would like to try a new approach in spite of the fact that most of our urologic residents are former undergraduate students of Tulane University

During the first year in medical school, the student is involved in learning a new vocabulary and new methods of study By the end of the first year, and certainly during the second year, clinical problems should prove stimulating

There are a number of courses with which urology could be effectively coordinated For example, the course in physical diagnosis is usually given during the second year under the direction of the department of internal medicine It seems reasonable to suggest that diseases that are of primary interest to the internist would be emphasized under this arrangement and that the internist's training might not enable him to spotlight problems that are of primary concern to one trained in another specialty

We believe, therefore, that urologic physical diagnosis should be given at the of medical schools prompted the American Urological Association to appoint a committee to study the status of undergraduate urologic training * Under the chairmanship of Ormond Culp a survey was made of 86 medical schools The manner in which urology was presented to the students, the status of the chief of the department, the relationship of urology to the other departments in the medical school and the time allotted to the course in the curriculum were all considered It was found that in only 20 per cent of the schools had the amount of time devoted to urology been reduced during the past ten years This was offset by the fact that there had been an increase in time allotment in 28 per cent of the schools

The present assignment is to consider what we are attempting to accomplish in teaching urology to medical students A simple answer would be to orient the student regarding common urologic problems as the department's contribution to the over-all effort to graduate competent physicians Fulfilling this obligation, however, is much more complicated and touches almost every department in the medical school

In planning the course in urology, we must consider the relationship of urologic problems to the basic sciences as well as to the clinical subjects Embryology, anatomy, physiology, pathology, endocrinology, bacteriology, and biochemistry must be included Internal medicine bears an inseparable relationship to the solution of many routine urologic problems

The departments of urology and radiology cannot be separated There are also many urologic problems that require close liaison with the departments of general surgery, obstetrics and gynecology, and pediatrics Practical planning, therefore, would suggest integration of many parts of the urologic program with other specialties in order that related subjects may be more clearly presented to the student To accomplish this requires much thought and cooperative planning

In the planning of any phase of undergraduate teaching, the three major factors of the educational system have to be considered, that is, the faculty, the student, and the time allotted to conduct the course Of primary importance is appraisal of the quality of the teaching in the various departments This appraisal should not be left entirely to the dean and the executive committee but should include critical self inventory of the individual instructors

The faculty To qualify for membership on a medical school faculty, the physician should possess a keen sense of responsibility to the institution and an obligation to render distinctive service in the performance of its functions He is a part of a system that is laying the scientific foundation for young men and women who have every right to expect that they will be prepared to assume positions of leadership in whatever field of medical endeavor they may enter after graduation

The student The present method of selecting students for admission to the medical schools appears to be reasonably effective Obviously, to every class a few are admitted who should not be permitted to study medicine There are

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The year that the student is introduced to urology is, in our opinion, of more than ordinary importance. For a number of years, urology at Tulane University has been a part of a block system given during a fixed period of the senior year. We have had ample opportunity to evaluate urologic teaching at this level and believe that it would be more effective to introduce urology to the student earlier by appropriate integration of the course with the other departments. We would like to try a new approach in spite of the fact that most of our urologic residents are former undergraduate students of Tulane University.

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We believe, therefore, that urologic physical diagnosis should be given at the same time and in co-operation with the department of internal medicine This includes instruction in how to attain a good urologic history and one that will give some indication as to the clinical condition present before any diagnostic procedures are undertaken The "long form," so popular in many institutions, is no substitute for a history based upon definite answers to well directed questions Also, in co-operation with the department of medicine the student should be introduced to the principles involved in urologic physical examination He should be instructed concerning the urologic diagnostic procedures that may be performed by the general physician and the findings that indicate the need for specialized studies that should be performed by the urologist

Didactic lectures There is considerable controversy concerning the value of didactic lectures in undergraduate medical education Urology, however, presents a unqiue opportunity to make these of interest to the student and effective in helping him understand the problems involved All parts of the urinary tract, including the renal circulation, can be visualized, and variations from the normal produced by pathologic lesions can be demonstrated

Lectures in urology can also be made more valuable if integrated with those of the respective departments involved For example, the great variety of congenital anomalies of the urinary tract should be more clearly understood by the student if given in conjunction with the course in the embryologic development of the urinary tract Other examples are endocrinologic disturbances with genital manifestations, metabolic problems, electrolyte imbalance and disturbances of circulation that may originate in the urinary tract

Other lectures may be given in co-operation with the department of obstetrics concerning urinary complications of pregnancy of importance to the general practitioner Such integration of lectures should contribute to a better over-all course for the student The remainder of the lectures may be given during the third or fourth year

Outpatient department Teaching medical students in the outpatient department is a challenge to planning and organization In the majority of teaching hospitals, the number of patients is far in excess of the number that can be utilized in a good teaching program In the large municipal hospitals it is difficult to limit the number accepted for treatment Under such circumstances, management of the department involves fulfilling the patient requirements on the one hand and instructing the students on the other Management of the ambulatory patient is important to the student, since this type will constitute the greater part of his practice after graduation In the majority of these, it is necessarily the function of the residents to administer to the patient needs From this group a small number of diversified urologic problems is selected for student instruction This includes a review of history taking which, at this level, involves patients with clinical problems of the genitourinary tract It provides an excellent opportunity to point out lesions that may be expected to present more or less typical symptoms, others that are asymptomatic in the early stages and still others that may be reflected through other systems, especially the gastrointestinal tract

From a large group of patients, it should be possible to select those with the more commonly encountered urologic lesions The symptoms and findings that lead to early recognition of malignant growths should be emphasized, especially the methods by which carcinoma of the prostate may be diagnosed while it is in a curable stage

Properly conducted, outpatient teaching should give the student good insight into the office management of private urologic patients With a show of enthusiasm on the part of the staff, the outpatient department should offer an excellent opportunity to interest the student in urology as a specialty Lack of interest by the staff can quickly destroy the effectiveness of the program Strict adherence to staff assignments to the outpatient department is important

Several plans of conducting outpatient teaching have been tried

1) Combining outpatient and inpatient service during the same period,

2) Giving inpatient clerkships in the third year and outpatient instruction in the fourth year and

3) Reversing the order of the second plan

A block system whereby all urologic teaching is confined to one period would obviously have to follow the first plan In a schedule that permits a choice, outpatient instruction given in the third year would appear to fit more correctly into the graded progress of the student

Inpatient clerkships Urologic teaching in the inpatient service requires the same careful planning that applies to all other phases of undergraduate teaching Three levels of instruction are being carried out on the same group of patients—one for undergraduate students and the other two for the interns and residents They cannot be combined Instruction for the student must remain at the undergraduate level

The inpatient service provides an opportunity for the student to observe more advanced urologic lesions and play a more active role in patient management than is possible in the care of ambulatory patients As a clinical clerk, he is usually the first person to see the patient, and his history becomes a part of the hospital record This should be reviewed by a member of the staff, constructive criticism offered and indicated revisions made The student is permitted to participate in the physical examination, carry out simple laboratory tests and observe the performance of the finer grades of urologic diagnostic procedures In the course of the patient's study, it is important to explain to the student all phases of the clinical problems involved, including interpretation of all findings He should be made to understand the etiology of each lesion under consideration, the pathologic changes that occur, the symptoms that are produced by it and the complications that may radiate from it All of these are essential to an understanding of the indications for the various therapeutic measures that are carried out The student is also able to follow the day-to-day progress of the patient and observe the results obtained from treatment There are two reasons for assigning students as clinical clerks during the fourth year One is that it is the logical sequence of progress in the educational program, and the other is the present trend toward abolishing the internship Finally, the patients assigned to the student should be diversified and limited to the number that can be adequately studied and still leave sufficient time for review of assigned reading pertinent to the problems under treatment

Moderator Higgins The discussion will be continued by Dr Carroll

Dr Grayson Carroll Mr Chairman, members I shall read the communication that was sent by Dr Cahill I do not assume to be a pinch-hitter for him I am merely a substitute You know there is a great difference

"To discuss intelligently undergraduate training in urology, one must appreciate the fact that all medical knowledge is in a continuous expanding sphere Therefore, the medical school in its effort to train its student body to serve the medical demands of the community must accept expansion in some subjects and contraction in others

"Urology as a specialty in medicine must be adapted to the space of time allotted in the student curriculum and an intelligent use of that time is the duty of the urological director To him also has been added the responsibility in the teaching of a training-residency graduate

"Before taking up an organization of a department of urology in a medical school, a short philosophical survey of the history of medical education since the last World War may be of interest The pre-medical education has been fairly well accepted as to subjects, but with the academic years varying with the medical schools themselves The curricula in most medical schools endeavor to cover the essentials in the four years allotted It is painfully crowded At the end of four years, if the student has been successful, he will receive a diploma of Doctor of Medicine

"The laws of most states read that he is not prepared to practice medicine although the diploma so suggests, but that he must take further training of at least one year of internship in a rotating or other type of internship He may take then his State Boards

"Is it not true that a large proportion of these students accept the fact that they are not to or they have not reached the competency they desire? They apply for and obtain that competency in a residency training of a varying number of years in order to so qualify

"The school of medicine actually arranges a curriculum to train basically the student as a general practitioner Perhaps, in truth, the larger part of a class is dreaming of a specialty and shaping their and the class's footsteps in that direction The older two-year internship was probably an excellent training for general practice, and there is a breath of talk about its revival

"How does urology stand in the present change? In some schools, its position has diminished in the hours allotted in the curriculum In others, it has remained the same, and in a few, it may be expanded My experience has been in the shrinking form for undergraduates and expansion for residency graduate programs The latter has been phenomenal in the United States as the following figures may show

"The last edition of the AMA Internship and Residency Number shows 6,845 medical graduates in 1956 For these, there were 867 hospitals with one-year internships for 11,616 doctors, leaving about 4,500 unfilled To help these, about 2,400 foreign doctors have been accepted Available after internship, there are 5,043 residencies, varying from two to five years Of these, urology had 221 one-year residencies with 70 per cent filled and a total of all residencies up to five years of 487 with 78 per cent filled

"Actually, the only place where urology is taught and training is adequate is in the residency programs The undergraduate school can only acquaint the student with the basic diseases and problems, diagnostically and therapeutically, and help him acquire the thinking to continue in good habits of study and progression in his education

"To organize a department of urology requires a director, who definitely should have what is considered academy tenure in the university He should have a complete choice in the naming of his staff and the distribution of their activities The size of the staff will depend upon many factors the size of the student class, the size of the hospital service to be used for teaching, the size of the outpatient department, the amount of research to be done within the department, and the available space for the same

"The director should have an adequate budget for his department, at least for the basic teaching of the students and for patient care Whether he should be on a fulltime status would depend upon the size of the service, the amount of money available to him to secure satisfactory living competency

"In these days of rising costs, the amount of a satisfactory competency would be debatable If he has not a full-time status, then there must be some satisfactory solution of the amount of time allotted to private practice in order to accomplish his living and the financing of his and the department's expenses

"His selection of an intelligent, industrious, loyal staff may make a success of his efforts If his selection has been poor, he may have difficulties The teaching of the clinicians is often best in the hands of the part-time man The research program, on the contrary, had best be under the guidance of full-time staff members The director should be energetic to join with his research staff in obtaining funds for their projects, because a few medical schools have their own very large research funds

"The department of urology needs close co-operation with other departments The tremendous use of x-ray in diagnosis makes it imperative that it should be within the department as part of the cystoscopy diagnostic unit The x-ray staff must co-operate in the teaching as well as in diagnosis

"Next, clinically, since there has been a gradual increase in pediatric urology, the close association of an interested urologic-minded pediatrician is of great value

"For many years, urology necessitated close association with the department of pathology To this has been added the most essential liaison of biochemistry and endocrinology, two most essential needs in modern urology The assignment of an interested member of each department to urology has been most productive in results

"Where should the urologist stand in determining the general policy of the school and the hospital? The director should be a member of the faculty and, in some schools, may rotate with other specialties on the executive committee. In the hospital, he should be a member of the medical board. His importance in the school may be determined by the number of hours of teaching allotted to undergraduates and the number of students in the graduate program. His standing in the hospital should be determined by the number of beds and percentage of urological patients in the hospital.

"His importance in the research of the school will probably be controlled by the activities of himself and his staff and the type and number of projects they can succeed in financing. Actually, the 'payoff' is the success of valuable and worthy reports. The acceptability of the projects for research must be based upon the space available and must be approved by the responsible university officers. Funds raised by the department in the hands of the university treasurer may be allocated for disbursement, according to the director and/or with the approval of the dean.

"The role of the department of urology as to the final examination of a student is one in which sympathetic accord must be given to the over-all estimation of the student. Failure of a major subject may prevent a student from passing. Failure of a specialty has been most often corrected by a special examination, separate and later than that of the others.

"Finally, should the department of urology be a separate department or under the control of the department of general surgery? My tenure of office was as director of a complete and separate department in the medical school in the university and in the hospital. We had a budget of our own, a staff appointed by the university on the director's recommendation. There was independence of action in raising funds and in allotting funds with the agreement of the dean's office.

"A large department, a staff of 16, a residency staff of eight or more, a large hospital service, all required an independent executive office. To add to the department of general surgery the executive work of urology would have been too cumbersome. In a smaller organization it could and can be more efficiently run as part of the department of surgery. So much would depend upon the personality of the directors involved to make for success or failure.

"Within recent years a survey was made with the hope of revision of the medical education program. An increase in studies in the pre-college age, a review of the college era was transferred to it of such studies in the school of medicine that do not require patient contact, an increase in the time in medical school for the specialties to fill in the gap left by the above transfer, some relief from the draft that hangs over the head of the student, or a change that would combine the armed service and civilian residency. As yet, no changes have occurred from this study."

MODERATOR HIGGINS: We will now hear the views of Dr. O. W. Hyman.

DR. HYMAN: Before I begin this let me say that I believe it is a good sign that this Association has taken an active interest in the quality of undergraduate medical training.

There seems to be a reasonable consensus that the purpose of undergraduate medical education is so to instruct the student that, when he is graduated, he will be *sufficiently well-informed in the major divisions* of medical practice — first, to arrive at an accurate diagnosis of diseases commonly presenting themselves and to recognize conditions which require more thorough-going analysis and, second, to treat successfully those conditions which do not require specialized experience and special equipment

Such a graduate can go into general practice with confidence or proceed to specialized training with an adequate background of general knowledge

The subject matter of the undergraduate medical curriculum is so arranged that from forty to sixty per cent of the time is allotted to instruction in the basic sciences The remaining time is, of course, assigned to the various clinical departments In the allotment of time practically all medical schools recognize as major divisions —internal medicine, surgery, obstetrics, and pediatrics Many add to these psychiatry or preventive medicine The importance attached to the remaining specialties as measured by time allotted varies from school to school and within very wide limits

Urology, of course, is one of these specialties The Culp report revealed that urology is quite generally recognized as an important factor in the training of the medical student I can present my conception of the best administrative status of the department by describing first the relationship of general administration to the department and, secondly, the internal administration of the department itself

What should be the relation of the dean to the department? The basic function of the dean is to provide leadership to the faculty in a co-operative effort so to arrange instruction as to give the greatest likelihood that students will come to graduation with the capabilities described heretofore

This requires the proper allocation of time to each department and the arrangement of instruction into the best possible sequence Especially is it the responsibility of the dean to secure proper balance of instruction among the departments and to be assured that each department gives the student a firm and adequate foundation in the subject matter of the specialty

This is a difficult job indeed Let us assume—in kindness—that the dean has a clear concept of the purpose of undergraduate education Let us assume also that he has achieved a high degree of objectivity and has evaluated quite accurately what each department should contribute to the training of the student

The discreet dean then appoints a curriculum committee The committee may be large or small Probably it will be composed of chiefs of divisions It should be properly balanced as between pre-clinical and clinical representatives

Since the chief purpose of medical education is to produce clinicians, clinical representatives should predominate (However, it is not the proper function of a member of the committee to forward interests of his division but rather he should bring to the solution of general educational problems the point of view resulting from his previous experience)

A good committee will keep in mind, as clearly as the dean, the basic purpose of the curriculum and will modify and improve the dean's program A poor committee at one extreme will be so complaisant as to serve no constructive purpose or at the other extreme have one or more members so aggressive and influential that they produce serious distortions of the curriculum as a result of misguided zeal for what they conceive to be the interest of their departments In deciding the best allocation of time, the curriculum committee serves a most useful function

There still remains, however, the delicate business of controlling the use of the time that the purposes of undergraduate training are accomplished If the training given by any department is inadequate, complaints from other departments are likely to arise promptly

There is no such protection, however, against over-training—that is, class requirements which seem to pre-suppose that the students will all become physiologists or internists or urologists instead of physicians

Each department has considerable incentive to attempt over-training The teacher's zeal to turn out as fine a product as possible may over-shoot the mark

There may be, occasionally, an attempt to impress upon the student indelibly—so that future recall may be assured—the surpassing learning and skill of the instructor The best protection against such abuse, of course, is that each teacher shall understand clearly the purpose and the limitations of undergraduate training

However, some degree of inspection and supervision must be exercised by department head, chief of division, and dean The ultimate responsibility lies with the dean

It is obvious that the burden on the dean is increased in proportion to the number of departments responsible directly to his office If the number is too great, his efforts to co-ordinate will be ineffective There will be a tendency for uncontrolled rivalries to develop and distort the student's training

It seems to me certain that twenty separate divisions are too many Five or six seem reasonable Urology would not be included in the restricted list I therefore believe that urology should be a department in the division of surgery

The chief of the division of surgery would then become responsible for the co-ordination of the surgical specialties with general surgery and with each other The chief could be a urologist or an ophthalmologist but he is much more likely to be a general surgeon

A decision must be reached as to which specialties are to be departments and which remain as sections of general surgery As I use the term, a department has a high degree of independence The head of a department controls the expenditure of money budgeted to the department He recruits and promotes members of his staff and controls assignments to duty He approves proposed research His hospital service and resident staff are separate under his control A section would be integrated with general surgery The well reorganized importance of urology to the general training of the student should guarantee to all departmental status

The head of the department of urology is the key to successful training in this field for the medical student His ideals and his clear understanding of the purposes and the limitations of undergraduate education will determine the quality of the program His good judgment will decide the assignment of lectures, inpatient service, outpatient service to the proper members of his staff so that each will be stimulated to his best efforts His stature will be measured by his success in recruiting his staff and securing their loyal and effective co-operation with him and with each other

It is the duty of the head of the department to assure himself that each member of his staff understands the purpose of the instruction assigned to him

It is necessary also that the head be sufficiently informed of the performance of each staff member to be assured that the courses are given as planned If the department has a heavy teaching program and a large hospital service, the administrative burden of the head will be heavy

In the selection of a department head, the primary consideration must be the personal qualifications of the man selected He must have a broad and clear-headed view of the purposes of medical education and the part of the department of urology in accomplishing these purposes He must command the respect of his staff and the students as a clinical urologist He must have the courage to carry through his program and the tact to secure the co-operation of his associates

Such a department head may be volunteer, half-time or full-time If he is a volunteer or part-time member of the staff he must have a deputy who may well be full-time, to assume much of the routine of administration and give to both staff and students the daily, on-the-job supervision that is necessary

If the department has an active research program, the staff members so engaged almost necessarily must remain in daily contact with the patients and the laboratories of the department Such a geographical full-time man could be either head of the department or deputy

Even if the resources of the medical college are sufficient to staff the urology department completely with full-time men, volunteer members of the staff will continue to make an indispensable contribution to teaching the undergraduate student This contribution will be chiefly at the bedside or in the outpatient department but such volunteers not infrequently are valuable additions to research teams

Most urologists, in their beginning years, have more time than patients Under such conditions, volunteer service at the medical college should be of mutual advantage The young urologist may be presumed to have up-to-date knowledge and training and eager enthusiasm The majority of such men will reduce their voluntary service or discontinue it as patient pressure develops

Others, however, develop a lasting interest in teaching and their value as teachers is enhanced steadily as they gain experience and prestige

In summary, I believe that urology should be a department in the division of surgery, that it should have a high degree of independence to carry on its program, that, under these conditions, it makes an extremely valuable contribution to undergraduate medical education, and that the dean and the chief of division must see that sufficient time and resources are available to realize the full potential of the department in medical education

MODERATOR HIGGINS The concluding remarks on the panel will deal with graduate training

Dr Piersol Urology, along with other specialties, has been subjected to many educational theories that from time to time have been proposed The committee of this Association which studied the status of urology in our medical schools presented a comprehensive, informative and critical report on undergraduate urologic training *

A review of the opinions thus obtained from groups of competent educators leads to the conclusion that many aspects of teaching specialties, including urology, continue to be controversial and that there is no unanimity of opinion as to the role of specialty training in undergraduate medical education Some hold that the teaching of specialties is out of place in the curriculum of a school of medicine, others that more time should be allocated to specialty training

Regardless of varying convictions as to the status of urology at the undergraduate level, there is agreement as to the validity of its inclusion in any graduate medical educational program, where some deans insist that it belongs

Aside from any discussion of when and where in medical education urology should be emphasized, it is widely recognized that as a specialty it occupies a unique position in that it is one of the least isolated of specialties since it commands the attention of general practitioners and cuts across, to a greater or lesser extent, every major subdivision of medicine Therefore, because of its admitted importance, urology merits the serious attention of those concerned with graduate medical education It is this aspect of urologic training that will be stressed in the following discussion

Ever since its organization in 1919, the Graduate School of Medicine of The University of Pennsylvania has adhered to the philosophy that satisfactory training in a clinical specialty requires at least a basic academic year of organized formal instruction, followed by a good residency program It is along these lines that the regular course in urology has been developed

In our Graduate School, many of the problems and difficulties that beset the teaching of urology to undergraduate students happily never have arisen From the earliest days of the School, urology has continued to be an independent department, administratively and educationally, with its own chairman and professor of urology, supported by a qualified faculty

Although entirely separate from general surgery, urology has co-operated closely with that department, in certain instructional areas urological students have been affiliated with those in surgery The time allotted to the course in urology is comparable to that in other clinical specialties, eight months

The urologic curriculum recognizes the close relationship between urology and other fields of medicine The student of urology is purposely exposed to appropriate subjects in medicine, neuro-psychiatry, pediatrics, radiology, endocrinology, etc

Obviously, chief emphasis is laid upon special instruction in urology, which is accomplished by the necessary number of didactic hours, supplemented by more hours of clinical and operative training, experience in technical procedures, such as cystoscopy, and cadaver surgery

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* *Journal of Urology*, 76 309-322, 1956

Clinical instruction has been carried on with little difficulty because hospital beds always have been available to the urologic service, not only at the Graduate School Hospital, but at a number of other affiliated institutions where ample, varied clinical material, controlled by members of the faculty, has been at their disposal for teaching Thus, one of the problems which in some medical schools appears to hamper the teaching of urology to undergraduates, fortunately, has not arisen

A unique feature of the Graduate School's urologic program deserves emphasis For the past 12 years and to some extent before that, all students enrolled in a basic course in any clinical specialty have been required to successfully complete a correlated course in the medical sciences It is around this course, presently of 217 hours, continuing throughout the academic year, that the various special curricula are developed

In addition to the economic, social, medical and even political changes which have occurred during the past quarter of a century, and have affected every aspect of American life, including medical education, there are two specific factors which have significantly modified graduate medical education

These are 1) the growing number of approved examining boards in the medical specialties and 2) the phenomenal growth of residency training programs throughout this country

Since its organization in 1934, the American Board of Urology up to June 30, 1956, has certified 2,195 physicians The total number of physicians certified, by all specialty boards of the United States, as of June 30, 1956, was 63,727 The largest number have been certified since the close of World War II From that time, including the present, physicians desirous of becoming specialists have been impelled by an overwhelming desire for certification

A requirement laid down by practically all boards is that candidates to be qualified for examination must, among other things, complete residency programs of varying duration in accredited hospitals The result has been an unprecedented demand for residencies in order to prepare for certification This trend became particularly acute after World War II, when a large number of physicians being discharged from the Armed Services were seeking opportunities to complete their specialty training

Whereas, in the early 1920's only a few hundred residencies existed in the United States, during the year 1954–55 there was available a total of 26,516 residencies in all fields Information recently obtained indicates that presently there are over 27,000 residencies in this country By no means are all these residencies filled

In 1955 the occupancy of all residencies throughout the country was 81 per cent During the year ending September 1956, throughout the United States there were 487 one to three year approved residencies in urology The percentage of this number filled was 78, a figure comparable to the average residency occupancy in all specialties, which last year was stated as approximately 80 per cent

To become a certified urologist, a physician must complete an approved residency program Since certification is a prerequisite for recognition in urology and any specialty, it is perplexing and hard to understand why there is such a percentage of unfilled residencies

The situation may reflect a lessened desire on the part of the physicians to confine their efforts to restricted specialties, because a similar situation exists in many other highly specialized fields It has been suggested that social and economic factors are responsible for this trend

It is certain the practice of urology, as well as that in other particular areas, has changed of late by reason of epochal therapeutic advances (sulfonamide, antibiotics, tranquilizing drugs), which have made possible the encroachment by the general practitioner upon special fields formerly dominated by specialists

A study of enrollment in the Graduate School over the past 30 years indicates the variations that have taken place in the urological group

The steady rise in the enrollment of urological students, which is noted from 1935 up until the entrance of this country into World War II, would seem to reflect increasing interest in obtaining certification by the American Board of Urology, which began to function at that time

The entire enrollment of the Graduate School dropped precipitately between 1942 and 1944 because of the hostilities then in progress At the conclusion of the War in 1945, enrollment took a sharp rise and during the next four years the group in urology, along with other divisions, enjoyed its greatest enrollment

This has been followed by a slow but consistent decline, which during the last four years in urology, as well as in other highly specialized fields, has reached a discouraging low This decline in the enrollment may well have been due in part to the growing interest of many physicians in general practice along with the termination of governmental subsidies available during the earlier post-war period The change in urologic practice, above alluded to, may be an additional factor

However, it is believed that the increasing need for residency training programs, which offer attractive financial advantages, is the chief reason for what appears to be a lagging interest in formal urological training

After careful investigation and study, it is our conviction that because of these changing trends in medical thought and practice and the growing popularity of and necessity for residency training programs, the time has come to modify our traditional basic eight-month courses The purpose of this change is to create more flexible courses which will enable those engaged in residency programs and who seek certification to obtain the type of medical education which will best meet their educational requirements

Practically all specialty-boards insist that applicants receive an adequate training and review of basic medical sciences Regardless of how efficient and valuable the clinical training of a resident in his specialty may be, it is generally conceded that the one aspect of preparation for certification which hospitals generally are unable to give adequately is a review of basic medical sciences It is true, in some of the larger hospitals connected with teaching institutions, that this may be done

Therefore, to meet the present situation, we have just completed a revision of all of our basic courses This revision will divide the basic eight-month course in clinical specialties into two semesters, the first, 16 weeks, from the latter part of September to the first of February, will be devoted to concentrated instruction in correlated medical sciences, formerly spread throughout the entire eight-month course

Not only will the students review the fundamental sciences, but each group will receive supplemental instruction in such basic sciences as are peculiar to their particular specialty The physician who successfully completes the basic science semester may elect then to continue with the clinical instruction offered during the later semesters or, if a resident, he may return to his hospital program there to complete such clinical training as is required of any particular board

This plan has been discussed with the Advisory Board for Medical Specialties Such comments as have been forthcoming have been encouraging The secretary of each certifying board now has in his hands copies of this new educational plan as it applies to his special field

It is hoped that when the various boards have an opportunity to study this new program, it will receive their approval and that a resident who elects to thus devote a semester to the study of medical sciences will not be penalized by having the time given to such study deducted from his period of residency training

This is particularly important since some of the boards in surgical specialties have objected to residents interrupting their clinical programs for an academic year in order to follow a didactic course in their specialties

It is further hoped that the Joint Accreditation Board for Hospitals will be receptive to this plan of having suitable residents sent away from their hospitals for a short period of training in medical sciences, without allowing such procedure to interfere with their accreditation of the institution concerned

It is believed that the adoption of such a flexible graduate educational plan should prove helpful and practical to physicians seeking certification and at the same time may aid in stimulating interest in urology as well as other specialties

MODERATOR HIGGINS I believe that most of the questions that were placed on the table prior to the beginning of the discussion were answered There are one or two that you would probably like to hear answered

One is "Dr Burns, should the urological staff be full or part-time?"

DR. BURNS I think that every department conducting both undergraduate and graduate programs should have at least one full-time staff member if funds are available The Division of Urology at Tulane University has always depended entirely on volunteer staff members We recognize the need for a full-time professor and are currently looking for one who will eventually assume the chairmanship of the department

MODERATOR HIGGINS The second question "Dr Carroll, should a part-time teacher receive cash compensation?"

DR CARROLL The trend now in teaching the specialties is to give instruction to smaller groups Therefore, more time of the part-time teacher is consumed than when only didactic lectures were given Then, too, the volunteer physician who teaches finds himself with less time at his disposal than he did previously

Therefore, it would seem advisable in some instances that the part-time teachers be paid for their services But I do not believe that as a group we are prepared to give up the traditional position that we have always held, as well as our obligation, to pass on our knowledge in medicine to the younger generation We still want to retain that opportunity to serve and, if possible, I believe we would prefer doing it that way

MODERATOR HIGGINS "Dr Hyman, is the enrollment of medical students decreasing in this country?"

DR HYMAN The enrollment is not going down, enrollment is going up, but the number of applications is going down To an individual applicant, however, it does not make much difference whether there are three times as many applicants as places or two times as many As long as there are more applicants than there are places there will be disappointments

When the number of applicants greatly exceeds the number of places, schools are able to select students who have better prospects of graduation At present the only yard stick for selection that is trustworthy is premedical grades Reliance upon other methods has proven so unsatisfactory that the safest method other than premedical average is to flip a coin

The number of acceptances is going up Medical colleges are increasing their enrollment and the number of colleges is being increased

MODERATOR HIGGINS Question for Dr Piersol "Is an integrated course in the medical sciences better than teaching the basic sciences as isolated subjects?"

DR PIERSOL This question is one which over the years has been discussed frequently, particularly in connection with the Graduate School, where until 1946, medical sciences were taught, as was usual, as separate and distinct entities, a course in pathology at one time, a course in physiology at another In 1946, under the direction of Dr Julius Comroe with the aid of Dr A Newton Richards, a correlated course in basic medical sciences was instituted This course is taught by men who are all doctors, even though they have advanced training in special basic scientific fields

Experience has shown that this plan is much more effective and practical, to our student physicians, because it enables them to *correlate better* the different aspects of a given subject, as for example, the effect of altered physiology upon the clinical picture

Personal experience convinces me that the teaching of clinical subjects closely *correlated with the medical sciences* has been the outstanding and most important contribution to graduate medical education This has been thoroughly and *favorably* discussed by the Association of American Medical Colleges There is unanimity that to correlate the basic medical sciences is a desirable procedure which involves, usually, considerable organizational change

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THE STRUCTURE OF AN UNDERGRADUATE TEACHING PROGRAM IN UROLOGY

ABEL J LEADER

Following the recommendations incorporated in the report of the American Urological Association's Committee to Study the Status of the Undergraduate Teaching of Urology in the Medical Schools,[1] the urology program at the Baylor University College of Medicine was reorganized The revised program has been in effect for two years This report describes in some detail the undergraduate teaching program in urology at the Baylor University College of Medicine

Increasing interest in the teaching of urology to medical students is indicated by the attention the subject has received at the last two annual meetings of the American Urological Association At its 1956 meeting, the Association heard a report from its Committee to Study the Status of the Undergraduate Teaching of Urology in the Medical Schools providing "a general panoramic view of the undergraduate urological instruction that prevails today, of the academic environments in which it is proffered, and of the educational trends that have evolved during the past decade " Although a principal stimulus had been provided for this study by the increasing concern expressed in some quarters that growing curriculum pressures were reducing the time allocations for the study of urology, as well as of the other surgical specialties, the Committee minimized the danger of this threat pointing out that at "87 per cent of the institutions surveyed, the urological services today still have reasonable opportunities to present creditable and well-balanced courses to undergraduates, despite recent concessions " Of more concern to the Committee was the character and quality of the teaching programs already in operation what appeared to be most needed was not a greater share of the medical student's time, but a more effective utilization of the time already devoted in most of the curricula to the study of urology One of its recommendations was that the American Urological Association could render a great service by sponsoring a panel or symposium at each annual meeting "where authoritative opinions could be aired, teaching methods could be compared, and projects for the future could be proposed " Probably as a result of this suggestion, the first symposium on the undergraduate teaching of urology was presented at the 1957 meeting of the Association

In the initial phases of its study, the Committee recognized the difficulties involved in attempting a comparative appraisal of the teaching methods and programs now in use in American medical schools, since these were too varied, complex, and too full of intangibles to permit statistical analysis for the purpose of arriving at valid conclusions For much the same reasons, it is almost impossible to develop even an idealized conception of a teaching program adaptable

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Based on a scientific exhibit at annual meeting of American Urological Association Pittsburgh, Pa , May 6–9, 1957

[1] Culp, O S , Burns, E , Flocks, R H , Higgins, C C , Hotchkiss, R S , Vest, S A and Weyrauch, H. M. The present status of undergraduate urologic training Report of the Committee to Study the Status of the Undergraduate Teaching of Urology in the Medical Schools J Urol , 76 309–322 1956 (Reprints of the report may be obtained from the American Urological Association, 1120 N Charles St , Baltimore 1, Md.)

to all medical schools Differences in the sizes of classes at the various medical schools, the diversification, volume, and character of the clinical material available to the uses of the teaching program, and the availability of capable urologists willing to spare the time from their private practices for teaching are all factors that modify the usefulness of a pre-tailored program in any medical school Of even more fundamental importance are the variations in the basic philosophies regarding the objectives of the undergraduate teaching in this specialty to which the urologists and the responsible administrative authorities of that particular medical school subscribe All of the foregoing gives added pertinence to the recommendations of the Committee that some medium be developed by which those concerned with the problems of urological education at the undergraduate level may communicate for the purpose of effecting a mutually beneficial interchange of ideas This suggests that expositional descriptions of the various undergraduate teaching programs that have proved effective would be helpful as preliminary to the more detailed study of teaching methods and techniques that should follow from other sources during the course of time

For the necessary background, it should be stated that the Baylor University College of Medicine is a privately-supported medical school located in Houston, Texas, an urban community of approximately one million population Both the medical school and the Texas Medical Center of which it is a part have been located in Houston less than two decades The strong traditions that develop with age and the support that accrues from a large body of loyal and devoted alumni have yet to develop fully Four of the seven major hospitals are directly affiliated with the medical school, and the urological services of two of the others are indirectly affiliated through a lateral agreement between Baylor and The Postgraduate School of Medicine of the University of Texas At last count, there were forty-five urologists in the Houston area, and of these more than half are on the clinical faculty in urology of the medical school All are either certified by the American Board of Urology or are eligible for such certification, the latter being a prerequisite for appointment Two months ago, a full-time instructor who had just completed his residency was added to the faculty

The effectiveness of the program to be described has been demonstrated in several ways For two successive years, the graduating classes have designated their course in urology as the best organized, most effectively presented, and best taught course of the clinical years Ten per cent of the seniors indicated their interest in following their internships with residencies in urology The instructors have been uniformly enthusiastic since the program as designed permits the individual instructor to make his contribution to the teaching effort in the minimum amount of time A feeling of mutual respect between the students and the faculty pervades all of the sessions and has been most rewarding to those who have planned the program Finally, the administrative authorities concerned with curriculum planning have responded to the suggestions of the senior class that the program be reinforced at the third year level Formerly, urological instruction in the junior year consisted only of eight didactic lectures given at weekly intervals by as many different lecturers this has now been expanded to include an additional sixteen hours of work with hospital inpatients, demonstrations, and "spot-seminars"

FUNDAMENTAL OBJECTIVES

The purpose of the program was not to make a competent urologist of every medical student or a physician capable of handling all urological problems without help but rather to provide him with an *understanding* of the basic principles of urology essential to a well-rounded physician It was recognized that for most medical students, their contact with urology during the clinical years in medical school might well be all they would have before entering upon the private practice of medicine The distinction had to be drawn clearly between what had to be done to provide students with this orientation in urological disease and what constituted *training in urology* The latter is a graduate discipline it is an extension of the educational process by which the resident, because of his special interest, not only broadens his base of understanding of the principles of urology, but he acquires familiarity, dexterity, and competence in the techniques peculiar to urology

The second fundamental objective of the program was to plan for the most judicious utilization of the time allotted As a result, the student soon becomes aware of the preciseness with which the program has been planned and of its sense of forward movement Similarly, the instructor, his teaching assignment clearly delineated as to content, but with no restrictions placed upon his ingenuity as a teacher, wastes no time Absenteeism on the part of both students and faculty alike has been remarkably low Our experience has been that a carefully planned program carried forward by instructors who are completely familiar with its over-all objectives as well as with their individual responsibilities to its successful implementation results in a student body that responds with enthusiasm and interest

A third consideration was that of keeping the demands on the individual instructor's time at the minimum consistent with accomplishing the objectives of the program, especially important since the introduction of the four-quarter system which makes it necessary to repeat the teaching effort at least four times during the academic year It seems appropriate here to quote again from the report of the Committee to Study the Status of the Undergraduate Teaching of Urology in the Medical Schools "Since urological teaching in 65 per cent of the schools is still dependent on part-time and volunteer instructors, it seems naive to insist upon changes that demand more and more time of those individuals who find it difficult to do justice to prevailing programs" Here again it has been our experience that a well-balanced and effective teaching program, since it utilizes the services of the teaching staff to the best advantage possible, actually has reduced the demands made upon the time of the volunteer instructors

Finally, some thought must be given to the need for recruiting to the urological residency training programs those students who show significant promise If their educational experiences in undergraduate urology have been made meaningful, there need be no vacancies in the residency training programs of the institutions at which these experiences were provided, nor need such vacancies be filled by candidates with less than adequate basic preparation

THE INSTRUCTOR'S MANUAL

In the development of an effective teaching program for medical students, three steps are considered essential The first is to project a clear picture of the program as a whole keeping in mind the objectives The second is to delineate, in as much detail as possible, the component parts of the program to insure its smooth and efficient operation Finally, what in our experience is most important, is to commit the entire detailed program to writing, leaving nothing to chance, to faulty memory, and to later argument Through the medium of a written program, an enormous amount of lost motion is eliminated Both the students and the instructor know when and where they are to meet and what the subject matter of the session is to be through reference to their printed schedules If preliminary preparation of an assignment is required of the student in the interest of making the class and group sessions more meaningful, this is a matter of written record that has been provided the student before the course begins Knowing in advance what the subject is to be, the instructor arrives 'primed' for his class The urological resident, acting as a binding force in his capacity as low-man on the teaching faculty, knows well in advance what teaching and clinical materials will be most helpful and makes certain that they are on hand when needed Overlap and repetition are avoided, duplication is eliminated The student soon becomes aware that absences from scheduled sessions are not without cost to him, and this too is not the problem it was formerly

At least one month prior to the beginning of the academic year, the Division of Urology prepares a multigraphed Instructor's Manual which is distributed to all members of the teaching faculty This is encased in a sturdy binder that is appropriately labeled to prevent its being accidentally discarded with pharmaceutical literature that arrives in the doctor's office mail This manual contains a covering letter that summarizes the accomplishments of the Division of Urology for the year just past and the program changes with the reasons for such changes for the academic year about to start, faculty assignments, student section lists, student schedules, and all other pertinent materials Instructors with major assignments (those meeting students in didactic sessions or correlation and quiz sessions in groups of twenty or more) are furnished with pictorial rosters of the students assigned to them, so that identification of the student may be made quickly from his photograph These are obtained from the Department of Visual Education and are of real value from the viewpoint that a student is no longer "the second man from the left in the third row" but is an individual with a name The student reacts favorably to this manifestation of personal interest

Provided with such a manual, the instructor knows at least one month in advance what the total teaching effort is to be, and that his own assignment is an important integral part of that effort During the past two years, instructors have gone to considerable pains to avoid failure to meet a class, but if an instructor cannot meet with his class, the procedure by which he obtains a substi-

TABLE 1 *Student assignment schedule, senior class (1957–1958)*

Hour	Monday	Tuesday	Wednesday	Thursday	Saturday
8 a.m to 9 a m	*Clinical case conference* 8th floor solarium Jeff Davis Hosp Dr Rape and staff	*Ambulatory treatment of urological patient* G U clinic second floor Jeff Davis Hosp	*Urological endoscopic diagnosis and surgery* Urological surgical pavilion 6th floor St Luke's Episcopal Hosp Students are to report to the 5th floor library	*Urological x ray conference* Room 204 VA Hosp Dr Deming and staff	*Urological correlation conference & quiz* Dr Leader Room 305 St Luke's Hosp
9 a m. to 10 a m					
10 a m to 11 a.m	*Diagnostic approaches to urology* 8th floor solarium Jeff Davis			*Urological ward walks* Urology ward VA Hosp Dr Deming and staff	
11 a m to noon	*Cystoscopy and retrograde pyelography* Cysto Rm 2nd Fl JD	*Techniques and interpretation of excretory urograms* Cysto Rm 2nd Fl. JD			
	Both groups A&B meet together for all Monday sessions.	Group B first 2 wks Group A 2nd two wks	Group A 1st 2 wks Group B 2nd 2 wks	Group B 1st 2 wks Group A 2nd 2 wks.	All students in surgical specialties quarter

tute is clearly stipulated A beneficial cycle is established the students, responding with interest and enthusiasm, stimulate the instructor to give something more

Representative pages from the Instructor's Manual are included to show the care with which time is utilized Table 1 is the senior class assignment schedule and indicates when and where the student is to report and for what purpose Table 2 is the faculty assignment schedule for the senior classes Only the first sheet is distributed to the students at registration both sheets are contained within the Instructor's Manual Table 3 is the senior class required reading list this contains the assignments in the text-book which form the basis for the Saturday morning informal discussions and quiz sessions Tables 4 and 5 are similar sheets prepared for the junior classes

The following paragraphs from the Instructor's Manual demonstrate the uses of this mechanism for the transmission of information to the faculty An example is shown of an announced change in the teaching program, together with the reasons for this change This is followed by a detailed description of the senior schedule

" The changes in the teaching program for the coming academic year reflect efforts to make urological instruction even more meaningful to the student As the program operated last year, many students received no significant orientation in urology until they had reached the last months of their medical school careers These students consequently attended other clinics during the third and fourth years unable to assay patients with associated urological disease It is to be expected that the modification of the teaching effort during the third year to be described below will overcome this deficiency to a considerable extent "

TABLE 2 *Faculty assignment schedule, senior course, academic year 1957–1958*

Day	Hour	Place	Subject	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter
Mon	8 a m to 10 a.m	8th floor solarium Jeff Davis Hosp	Clinical case conference	Drs Rape Thomas, and staff	Drs Rape Robinson and staff	Drs Rape, Fish and staff	Drs. Rape, Alexander, and staff
	10 a.m	8th floor solarium, Jeff Davis Hosp	Diagnostic approaches to urology	Dr Thomas	Dr Robinson	Dr McDonald	Dr Leifeste
	11 a.m.	Cystoscopy room 2nd floor Jeff Davis	Cystoscopy and retrograde pyelography	Dr Thomas Dr Scott	Dr Guinn Dr Scott	Dr Arnold Dr Scott	Dr Seybold Dr Scott
Tues	8 a.m to	G U clinic, 2nd floor Jeff Davis Hosp	Ambulatory treatment of urological patient	Drs McDonald, Boren, Stahl	Drs Leifeste Pranke Grabstald	Drs Hutchins, Guinn, Grimes	Drs. Arnold, Hutchins Wolf
	11 a m	Cystoscopy room 2nd floor Jeff Davis	Techniques and interpretation of excretory urograms	Dr Hutchins	Dr Pranke	Dr Grabstald	Dr Guinn
Wed	8 a m to noon	Library, 5th floor St Luke's Hosp	Urological endoscopic diagnosis and urological surgery	Drs O'Heeron and Fish	Drs Guthrie and Seybold	Drs. Shearer and Hutchins	Drs Powell and Rape
Thurs	8 a m to noon	Room 204 VA Hosp	Urological x ray conference and urological ward walks	Dr Deming and staff	Dr Deming and staff	Dr Deming and staff	Dr Deming and staff

1st quarter Sept 16–Nov 9 second quarter Nov 11–January 18, third quarter Jan 20–March 15 fourth quarter March 24–May 17

Holidays Nov 28 (Thanksgiving Day) Dec 20–Jan 1 (Christmas holidays) March 16–23 (spring vacation) April 21 (San Jacinto day)

Instructors are requested to provide their own substitutes in the event that they cannot meet with their groups for any purpose

UROLOGY AT THE THIRD YEAR LEVEL

"Eight didactic lectures are given during the course of each eight-week quarter to two groups of junior students each such group is a 'section' and comprises from ten to thirteen students In each instance these lectures are followed by a two-hour period on the urological ward of the Veterans Administration Hospital In effect, a substantial part of the work previously reserved to the senior class is now to be offered as junior class instruction This will allow for the revision of next year's senior curriculum to a more advanced level This year, all eight of the didactic lectures are to be given during the course of any one quarter by a single instructor, instead of eight different lecturers as was the case last year It is expected that this will result in the development of a more integrated course and consequently more sustained interest on the part of the students

"The purpose of the didactic lectures is to bridge the transition insofar as urology is concerned between the studies of the pre-clinical years and the actual principles involved in clinical urology Emphasis is at all times to be placed on the interpretation of urologic disease in light of the basic sciences studied earlier

TABLE 3 *Reading assignments, senior class, academic year 1957–1958*

Textbook Campbell, Principles of Urology, W B Saunders, 1957 This book is procurable from the Medical School Bookstore The reading assignments for each session are indicated below The student's attention is directed to the section in the textbook entitled Questions (p 573–592, incl) since he is expected to be able to answer these questions during the Saturday morning Urological Correlation Conferences and Quizzes

Collateral readings are optional because of the inclusiveness of the textbook assignments, but for the interested student inspection of the following reference books is suggested

Campbell, M F *Urology,* 3 vols Saunders, 1954
Lowsley and Kirwin *Clinical Urology,* 2 vols Williams & Wilkins, 1956
Barnes and Hadley *Urological Practice,* Mosby, 1954
Braasch and Emmett *Clinical Urography,* Saunders, 1951
Hinman *Principles and Practices of Urology,* Saunders, 1935
Narath *Renal Pelvis and Ureter,* Grune and Stratton, 1951
Davis *Mechanisms of Urological Disease,* Saunders, 1953

All sessions begin promptly at 8 a m in Room 305 (Seminar Room) on Saturday mornings at the St Luke's Episcopal Hospital, and roll-call may be anticipated

Session 1 Sept 21, Nov 16, Jan 25, March 29
INTRODUCTION TO CLINICAL UROLOGY
Reading assignment Textbook, pp 1–72

Session 2 Sept 28, Nov 23, Feb 1, April 5
APPLIED ANATOMY AND PHYSIOLOGY OF THE UROGENITAL TRACT
Reading assignment Textbook, pp 72–122

Session 3 Oct 5, Nov 30, Feb 8, April 12
EMBRYOLOGY AND ANOMALIES OF THE UROGENITAL TRACT
Reading assignment Textbook, pp 122–213

Session 4 Oct 12, Dec 7, Feb 15, April 19
INFECTIONS OF THE URINARY TRACT
Reading assignment Textbook, pp 213–266

Session 5 Oct 19, Dec 14, Feb 22, April 26
THE MALE REPRODUCTIVE TRACT
Reading assignment Textbook, pp 266–379

Session 6 Oct 26, Jan 4, March 1, May 3
GENITO-URINARY INJURIES URINARY CALCULOUS DISEASE
Reading assignment Textbook, pp 379–444

SESSION 7 Nov 2, Jan 11, March 8 May 10
TUMORS OF THE UROGENITAL TRACT
Reading assignment Textbook, pp 444–511

SESSION 8 Nov 9, Jan 18, March 15, May 17
UROLOGY IN THE FEMALE
Reading assignment Textbook, pp 541–566

EXAMINATIONS

1) Weekly spot quizzes These will be given at the Saturday morning sessions at the option of the instructor, and will be based on reading assignments

2) Final written examination This is an open-book true or false, multiple choice, and fill in type of examination covering all aspects of the materials covered in the course Copies of the examination will be distributed to the students at the end of each quarter and are to be taken home and completed in accordance with the instructions on the face-sheet of the examination

3) Final oral examination This is given to groups of 5–6 students following the completion of the course on the dates indicated on the appended senior class list This examination will encompass the interpretation of urological roentgenograms, the material contained in the written examination, and the identification of gross specimens demonstrating genitourinary pathology

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PRIZES

Attention of the students is directed to the following urological prizes which may be awarded annually

The Frank Coleman Hamm Prize in Urology This prize is awarded annually to that senior student who in the opinion of the urological faculty has demonstrated the greatest aptitude in the interpretation of urological roentgenograms during the course of his clinical training

The Herman L Kretschmer Prize in Urology Awarded annually to that senior student who during the course of his clinical years first makes a diagnosis of operable ("early") carcinoma of the prostate, subsequently proved

TABLE 4 *Assignment schedule for junior class lectures, academic year 1957–1958*

Textbook Textbook of Urology, Victor F Marshall, Hoeber Harper, 1956 This book is procurable from the Medical School Bookstore Assignments in the book are indicated for each session, and the readings are to be accomplished by the student *prior* to the session dealing with the assigned subject

Time and place of lectures To allow for adequate travel time from Jefferson Davis Hospital to the Veterans Administration Hospital, the classes will commence promptly at 2 30 p m each Tuesday in Room 137 at the Veterans Administration Hospital This room is located immediately off of the main entrance corridor leading to the elevators and is immediately across from the elevators Fifty minutes is allotted to each lecture

Following this lecture, the students will spend an additional two hours at the Veterans Hospital, either on the ward, the cystoscopy room, or the treatment room An additional assignment list for this ward work is appended

Session 1	Introduction THE LANGUAGE OF UROLOGY Assignment, pp 1–22
Session 2	OBSTRUCTION-INFECTION Assignment, pp 23–41
Session 3	OBSTRUCTIONS IN THE UPPER URINARY TRACT Assignment, pp 42–56
Session 4	DISEASES OF THE PROSTATE, URETHRITIS Assignment, pp 57–74, 146–156, 213–223
Session 5	URINARY CALCULI Assignment, pp 75–91
Session 6	CONGENITAL ANOMALIES Assignment, pp 92–110
Session 7	UROGENITAL TUBERCULOSIS, MISCELLANEOUS DISEASES Assignment, pp 122–135, 173–183
Session 8	NEOPLASMS OF THE URINARY TRACT Assignment, pp 194–212, 224–229

Detailed discussions of the subjects of Trauma and the Neurogenic Bladder are reserved for the senior sessions Because these entities will be encountered on the ward during the junior year, reading of these chapters is recommended

Therapeutic management should be discussed only briefly and then only if such discussion is necessary to the completeness of a particular case presentation "

UROLOGY AT THE FOURTH YEAR LEVEL

"As with the junior class, the senior class is divided into 8 sections of 10–13 students These sections are further divided into groups A and B The entire section meets as one group on Mondays, but on Tuesday, Wednesday, or Thursday, only group A *or* group B meets with the instructors as indicated in the appended assignment schedule Thus groups A and B attend *four* sessions of the Monday meetings, but only *two* of the meetings scheduled for Tuesday, Wednesday, or Thursday For the first two weeks of the month that the section is assigned to urology, group A is in attendance on Monday and Wednesday, while group B attends on Monday, Tuesday, and Thursday At the end of two weeks, the groups switch their days, so at the end of the month, each group has had equal time

TABLE 5 *Student assignment schedule, junior class, academic year 1957–1958*

All students in both sections in each quarter will meet in Room 135, VA Hospital, on Tuesdays at 2 30 p.m promptly for a didactic lecture, which will occupy the first of three 50 minute periods The two periods following will be spent by the groups indicated in the activities listed below

1st quarter Sept. 16–Nov 9 2nd quarter Nov 11–Jan 18 3rd quarter Jan. 20–Mar 15 4th quarter Mar 24–May 17	Group 5 A Group 7 A Group 1 A Group 3 A	Group 5 B Group 7 B Group 1 B Group 3 B	Group 6 A Group 8 A Group 2 A Group 4 A	Group 6 B Group 8 B Group 2 B Group 4 B
Session 1				
Period 2	Ward work	Ward work	Conf No 1	Conf No 1
Period 3	Ward work	Ward work	Conf No 2	Conf No 2
Session 2				
Period 2	Conf No 1	Conf No 1	Ward work	Ward work
Period 3	Conf No 2	Conf No 2	Ward work	Ward work
Session 3				
Period 2	Ward work	Ward work	Conf No 3	Conf No 3
Period 3	Ward work	Ward work	Conf No 4	Conf No 4
Session 4				
Period 2	Conf No 3	Conf No 3	Ward work	Ward work
Period 3	Conf No 4	Conf No 4	Ward work	Ward work
Session 5				
Period 2	Ward work	Ward work	Conf No 5	Conf No 6
Period 3	Ward work	Ward work	Conf No 6	Conf No 5
Session 6				
Period 2	Conf No 5	Conf No 6	Ward work	Ward work
Period 3	Conf No 6	Conf No 5	Ward work	Ward work
Session 7				
Period 2	Ward work	Ward work	Oral quiz	Oral quiz
Period 3	Ward work	Ward work	Oral quiz	Oral quiz
Session 8				
Period 2	Oral quiz	Oral quiz	Ward work	Ward work
Period 3	Oral quiz	Oral quiz	Ward work	Ward work

CONFERENCE SUBJECTS

Conf No 1	Room 204	Review of Male G-U Anatomy and Physiology
Conf No 2	Room 204	Introduction to Urological Roentgenology
Conf No 3	Room 204	Normal and Abnormal Renal Function as it Relates to Urology
Conf No 4	4th Fl Cysto Rm	Physiology of Micturition Demonstration of Cystometry
Conf No 5	4th Fl Cysto Rm	G-U Trauma Practical Exercises in Evaluation
Conf No 6	Room 204	Practical Diagnostic X-Ray Conference

Teaching staff For the second and third periods, instruction will be given by Drs Deming, Lage, Scott, and Lavander during all four quarters In addition, Dr Grabstald is assigned to this staff during the first quarter, Dr Grimes, the second quarter, Dr Pranke the third quarter, and Dr McDonald, the fourth quarter

“Mondays Groups A and B meet together

“*8 a m to 10 a.m Urological case conference* Place 8th floor solarium, Jefferson Davis Hospital The house staff presents interesting cases admitted to the urological service during the preceding week These are discussed by the instructor and the other members of the attending staff present with preliminary interpretation of the urological x-rays by the students present Where indicated, short talks are given by the instructors present to clarify the problem under discussion The entire conference is slanted to the student's capabilities Four sessions

"*10 a m Diagnostic approaches to urology* Place 8th floor solarium, Jefferson Davis Hospital Four sessions In sequential order, the following subjects should be discussed with and demonstrated to the students, using whatever illustrative materials considered necessary

"a) The rectal examination The great significance of this examination both in urology specifically and in clinical medicine generally should be discussed in detail What is a "normal" rectal examination? The limitations of the rectal examination should also be explained

"b) The urethra Discuss the anatomical components of clinical significance, normal calibration, and demonstrate commonly employed urethral instruments Discuss briefly the pathogenesis and findings of urethral stricture, meatal stenosis, and other narrowings of the urethra

"c) The cystoscope Demonstrate the commonly employed diagnostic cystoscopic instruments, as well as those instruments used in endoscopic surgery Describe and demonstrate ureteral catheters, bulbs, bougies, baskets, stone loops and the like and explain their uses Have the students practice the use of the visual instruments on the mannikin bladders provided for this purpose

"d) The scrotum and scrotal contents The normal testis, epididymis, and cord structures should be shown Whenever possible, the resident will present one or more cases of scrotal disease The distinguishing features and relative incidence of "orchitis," epididymitis, and testicular torsion should be explained The transillumination of scrotal masses and the salient features of testicular tumors will be discussed

"e) Retrograde pyelography Its uses and indications are to be discussed although the actual demonstration of the techniques involved is reserved for the following hour Normal retrograde pyelograms are to be shown, as well as classical examples of pathology demonstrable by this technique These films will be provided for the instructor by the resident

"f) Excretory urography Discuss the historical background of the technique, the physiology of 'dye' excretion, contrast media, routes of administration, indicate the uses and limitations of the procedure Consider 'delayed films' and the value of excretory urography in the differential diagnosis of acute abdominal conditions Demonstrate also the 'post-voiding film' as a means of determining the residual bladder urine

"g) Aortography Discuss the techniques and usefulness in the delineation of renal tumors, renal cysts, aneurysms, etc

"h) Retroperitoneal pneumography Discuss the usefulness of the procedure in the delineation of obscure renal outlines, renal and extrarenal masses, adrenal tumors, and explain the methods of perirenal and presacral air insufflation

"*11 a m Correlative cystoscopy and retrograde pyelography* Cystoscopy room, Jefferson Davis Hospital Four sessions Each of two instructors will demonstrate the performance of diagnostic cystoscopy and retrograde pyelography on patients provided for this purpose by members of the house staff to groups of 5–6 students The methods employed for obtaining differential specimens for microanalysis and bacteriological study, as well as the use of indigo carmine and phenolsulfonphthalein for the determination of kidney function should be shown If possible, show the uses of biopsy instruments, the cystoscopic manipulation and extraction of a ureteral stone, etc In order to permit the greatest number of students to benefit from these examinations, general or saddle-block anesthesia should be used, when possible At least one of these sessions should be devoted to the demonstration of a diagnostic study on a patient from the pediatric service. If the procedure is to be done under anesthesia, the anesthetic should be given early enough to allow for the completion of the examination in the time allotted

"Tuesdays Group B first two weeks, Group A last two weeks

"*8 a.m to 11 a.m Ambulatory treatment of the urological patient* Each of the instructors will assume responsibility for the instruction of 1–2 students who are to be assigned to patients whose complaints and physical findings they are to elicit and evaluate Informal discussions concerning commonly encountered urological problems as seen in office practice are to be encouraged. Urological problems peculiar to the female are also to be demonstrated If time permits, demonstrate the passage of sounds, catheters, filiforms, etc and allow the students to do this as well Keep the students interested, occupied, and discourage excessive coffee-breaks! Two sessions

"*11 a m Technique and interpretation of excretory urograms* This study is to be demonstrated on a patient previously scheduled for this procedure Discuss its uses and limitations, the patient's preparation for the study, tests for sensitivity, and methods of administering the medium At the first of these two sessions, suggest that one of the students volunteer as the subject at the next session this will stimulate a personal interest in the procedure, as well as in the findings Two sessions

"Wednesdays Group A first two weeks, Group B last two weeks

"*8 a m to noon Urologic endoscopic diagnosis and urological surgery* Students assemble at 8 a.m in the fifth floor library at the St Luke s Episcopal Hospital, where they meet with the instructors for orientation and assignment Students are to be assigned either singly or in pairs to the individual urologists at work in any of the seven operating rooms in the urological surgical pavilion They may be given instruction in group concerning the open surgical procedures to be done during the course of the morning All are to wear scrub suits It is suggested that the 8 instructors-in-charge, two of whom are to serve during each quarter of the academic year in the responsible capacity, will co-operate with each other by reserving the posting of their own cases of instructional merit to Wednesday mornings The complete co-operation of the operating room nursing staff and of the anesthesiologists has been assured us to allow the posting of the maximum number of cases It is hoped that all other urologists at work will similarly give their assistance to the instructors in charge The resident staff in urology at St Luke's will participate in the educational features of these sessions by detailing the history and demonstrating the x-rays of the patients scheduled Two sessions

"Thursdays Group B first two weeks, Group A last two weeks

"*8 a m to noon Urological x-ray conference, urology ward-walks* These are conducted at the Veterans Administration Hospital by the hospital's chief of urology and his staff Case presentations of interesting and instructive problems of hospital patients will be presented, followed by pyelogram clinics devoted to consideration of major urological disease entities such as neoplasm, trauma, tuberculous and non-tuberculous infections of the urinary tract, etc Ward walks follow after a short intermission, and the principles of preoperative and postoperative care of urological patients will be discussed Two sessions

"Saturdays All seniors in the surgical specialties quarter Eight sessions

"*Place Room 305, St Luke's Episcopal Hospital Time 8–9 a m Urological correlation conference and quiz* This one-hour session is devoted to an informal discussion of the high points of the reading assignment in the text-book, to the oral quizzing of the students with respect to the clinical problems touched upon during the week, and to the clarification of such information as still remains obscure in the minds of the students It is conducted throughout the year by the divisional head, providing the latter with a means of checking on the effectiveness of the teaching from week to week "

STUDENT PERFORMANCE AND EXAMINATIONS

Although examinations are usually considered the most important method in use for evaluation of student accomplishment, at the level of the fourth year precise mathematical grading seems to serve little purpose At the third year level, one or two questions in urology are included in the written examination given by the Department of Surgery, but primary importance is attached to the student's day-to-day performance in the course

The seniors are given a type of examination that has been very favorably received This is truly more of an exercise than an examination and consists of approximately 200 questions of the true-or-false, multiple choice, and fill-in types These are distributed to the seniors at the end of the quarter in which the work in urology has been completed The students are then allowed to take the examination home with them for 72 hours, during which period they complete the exercise using any notes or text-books they may wish to use The only stipulation made, and the student signs a certificate incorporated into the face-sheet of the examination for this purpose, is that the student pledges that he has completed the exercise by himself It is pointed out that a group effort serves only to defeat the principal aim of the examination self-education Each of these questions incorporates a point important to the urological orientation of the physician and is thought to represent a pinch-graft from which the student extends his knowledge of urology The avidity with which medical students look for information in capsule form, or as "nuggets" or "pearls" as they are termed is well known

These examinations are graded quickly by the secretary of the divisional head employing a master examination containing what are accepted as correct answers and are subsequently used as the basis for part of an additional two-hour oral "final" quiz that is given to groups of 5–6 students on a Wednesday evening following the completion of the course Since the senior class consists of 8 sections, each of which is in turn divided into two groups of 5–6 students each, an additional 32 hours of effort is required of the teaching staff This is not an unpleasant chore, and the junior members of the faculty seem to enjoy participating in them At these final oral quizzes which may be scheduled for an evening some months after the student has completed his work in urology, the emphasis is still upon teaching, and not primarily upon the evaluation of student accomplishment and retentiveness Gross specimens demonstrating readily apparent diseases of the genitourinary organs from the Department of Pathology and interesting urological roentgenograms are also used for the purposes of informal quizzing Hypothetical case presentations such as the following are used to develop in the student the capacity for understanding the genesis and the mechanisms of urological disease In such cases, the correct diagnosis is only part of the answer the student must be able to justify his diagnosis through analysis of the symptoms and findings

"The patient is a 32-year-old white male carpenter who appears to be chronically ill, but admits to being sick for only ten days, getting progressively worse His past history is unremarkable except for a badly infected foot some three months earlier His temperature is 100 6F and the white blood cell count is 16,300 His urine appears to be grossly clear, and microscopically shows only a few pus cells per high powered field Gram stain of the urinary sediment reveals coccal forms in chains and clumps

"When first seen, he stands with his thorax forward, bent at the waist On the examining table, he is seen to lie with his right leg drawn upward, flexed at the hip, and efforts on the part of the examiner to straighten the leg meet with strenuous resistance from the patient An indefinite fullness is felt in his right flank and right upper quadrant Moderate costovertebral angle tenderness to fist percussion is present on the right

"The scout film of the abdomen shows no opaque shadows compatible with urinary calculi but the entire right side of the abdomen is relatively more opaque than the left, and has a homogeneous appearance similar to that of ground glass The right renal outline and the transverse processes of the vertebral bodies on the right are obscured A scoliosis with its concavity toward the right is apparent on all films Following the intravenous injection of contrast substance for the purposes of excretory urography, the architectural details of the collecting systems are normal bilaterally despite the apparently greater density of the contrast substance on the left "

All in all, the spirit that prevails is one of camaraderie and the experience is not intended to be traumatic to the student It is unusual for one of these sessions to come to an end without a spontaneous expression of appreciation from the students to the instructors for their interest and effort

As an added stimulus to continuing interest in urology, two prizes are awarded annually at the senior class banquet at the close of the academic year These have been established by members of the teaching faculty to honor distinguished teachers of urology The first such prize is given to that senior student who has demonstrated the greatest aptitude for the interpretation of urological x-rays, the second prize, to that senior who during the course of his clinical years first makes diagnosis of early carcinoma of the prostate, subsequently proved In both instances, the prizes are sets of standard urological reference books

UNDERGRADUATE UROLOGICAL TEACHING, AND RESEARCH AND CLINICAL INVESTIGATION

At first thought, there would seem to be but little relationship between an effective undergraduate teaching program and the programs of clinical investigation and research necessary to the continuing vigor of the specialty of urology, and in the minds of many, these are considered almost antithetical Closer examination will reveal that a good teaching program and a well-balanced research program have an immediate reciprocal relationship The medical school is the principal source of the newly discovered truths that are applicable to the everyday practice of medicine, and experimental research and clinical investigation are the means by which the medical school fulfills its fundamental obligation for the advancement of knowledge The properly stimulated inquiring minds of the students, fresh and possibly naive in their approaches to what to them are new spheres of knowledge, represent a constant challenge to the validity of traditionally accepted empirical ideas, methods, and techniques Thoughtful teachers recognize and nurture this quality in students, although the pressures of time may necessitate the use of teaching techniques that are justifiably subject to criticism as "spoon-feeding" The gadfly in today's senior class may well become the most prolific of tomorrow's investigators in urology And it is a truism that "he who teaches, learns" for the conscientious instructor finds himself engaged in a continuing critical re-examination of his subject matter Certain qualities seem to be common to all who are considered the best teachers They are usually men with clear-cut educational ideals, exacting habits of thought, enthusiasm for learning, and an attitude of critical open-mindedness These qualities both cultivate and are cultivated by productive investigation, in which the good teacher, whatever his subject, must almost inevitably become involved To him the term "research" no longer connotes a nebulous and fanciful other-world reserved to the inarticulate and introverted in which he has no part Instead, it becomes a broad avenue upon all who will can travel for the purpose of adding to the competence of man to live in his environment It is scholarship a continuing search for truth Our training programs and our teaching programs must aim to make of our students and instructors alike the scholars that will enrich and ennoble our specialty and our profession

SUMMARY

At the 1956 annual meeting of the American Urological Association, the Committee for the Study of the Status of the Undergraduate Teaching of Urology in the Medical School stressed the need for both the development of effective teaching programs in urology for medical students, and for some medium by which mutually beneficial information concerning such programs, teaching methods, and teaching techniques could be disseminated to all urologists concerned with the problems of undergraduate instruction In response to these suggestions such a program was developed and this essay, containing in some detail the structural planning of the undergraduate teaching program in urology at the Baylor University College of Medicine has been prepared By such objective standards as are available, this program has demonstrated its effectiveness Its principal advantages are in the careful utilization of the time allotted to the study of urology and the reduced demands made upon the time of the volunteer teaching faculty as a result of precise programming Considered indispensable in the development of such a program is a written manual for instructors that clearly states the over-all objectives and defines the individual instructor's responsibilities

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UROLOGY—AS OTHERS SEE IT

GEORGE C PRATHER

All of you, accomplished veterans in the field of urology, have mature concepts in regard to the scope of, techniques in, and training for proficiency in this specialty No doubt most of your opinions are valid because of your close attention to and thoughts about these problems over a period of many years However, before final conclusions are reached on these matters, it might be wise to know what those in a larger field of medicine think about our specialty, urology

I happen to have some information on this point in the form of answers to inquiries by a distinguished general surgeon, who acted as chairman of a committee to determine whether the urological service in a large general hospital should be continued or abandoned

Just by chance at a dinner one evening my friend, the general surgeon and committee chairman, asked me if I would be interested in seeing the replies of 22 outstanding surgeons and professors of surgery concerning this problem Feigning mild interest at that moment, I lost no time in obtaining the bound volume of letters the very next day for a careful digest of the opinions expressed

Thus you have the background and basis for Urology—As Others See It Permission has been granted by my surgical friend to use quoted statements, but of course the names of those responsible for the various opinions will be omitted

Has urology become a firmly established specialty? Are urological departments or services in a large hospital justified? If so, what factors have been responsible and what factors will determine the future of urology as a specialty?

Sixty per cent of the outstanding general surgeons who replied to these points were convinced that urology was justifiably established as a specialty and would continue to be so This point of view was expressed positively by "In brief I think that general surgery should not absorb urology and that the specialty will continue to be an important one if it is given a good deal of freedom ", and "For a long time to come I believe the major part of G U surgery will be done here by G U men ", or "I do not think we can abolish specialization since it is so firmly established and I think it has in general, justified its existence "

Twenty per cent were less affirmative in their opinion of urology as a specialty To quote "I think that the specialty of urology as a whole has insulated itself to a point where the broad influences of medicine and surgery no longer make contact ", or "The time will not be too distant when we shall have to consider whether urology will not suffer the same fate that laryngology has suffered ", or "In short, I favor preserving the identity of urology as a specialty but am by no means sure that I am right "

Twenty per cent were definitely negative in their opinion that urology should be a specialty A few sample statements are "I actually hope that you will make it a part of general surgery, because I actually believe such an arrangement would be advantageous to the patient as well as physician ", or "I feel that the

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Read at annual meeting of American Association of Genito-Urinary Surgeons, Hot Springs, Va, May 1–3, 1957 more we can get the subspecialties of surgery back into the field of general surgery, the better off everyone will be ", or "It seems to me a very good case can be made for reuniting urology and general surgery if a practical basis for doing so can be found "

From the quoted views expressed and tabulated it is evident that the majority of the general surgeons who replied have respect for and believe in urology as a surgical specialty, although a number regard our outlook as too narrow for the welfare of all The majority favor a urological service in hospitals for the care of urological patients

If one attempts to determine what has been responsible for the development of our specialty let me quote what our surgical friends have to say "Doctor X and his associates over the past years have had a continuing program of research that certainly would not have been carried out had they not had their special interest in that field ", or "The urologist commands a diagnostic and therapeutic tool—the cystoscope—which is not available to others He thus is in the enviable position of controlling both medical and surgical phases of his specialty ", "Medicine, surgery and now urology are proving grounds for basic physiological concepts ", or "In the field of investigation it is true that urology overlaps medicine, physiology, pathology and general surgery but I rather think that several groups approaching our common problems from different viewpoints may accomplish more than if they all work together "

I believe it is evident that two factors have been important in establishing urology on firm ground Research, both basic and clinical, has produced great respect for urology in the minds of those who are well informed about problems relating to the urinary tract If a specialty does not reveal new facts about the diseases or conditions in its field and thus contribute to the knowledge of medicine in general, it is derelict in its responsibilities

The second important factor in the development of urology as a specialty is of course the special instruments which are available for both diagnosis and treatment Skill in their use, by training and experience, commands respect from those not intimately familiar with these facilities

An important question in many hospitals today is the relation of the urological department or service to that of the general surgical service How do our friends in general surgery feel about this?

As one might expect, there is rather uniform opinion in the replies that I have studied All feel that urology should be autonomous in the care of urological patients, but that from an organizational standpoint, the general surgical division should correlate all the surgical specialties and really be the boss Let me quote some opinions—"The urological department should be an integral part of the division of surgery and participate in the surgical program ", "In its organization, urology should be a section of general surgery, both from the standpoint of hospital administration and of the university Some narrow-minded urologist may feel that this arrangement detracts from the prestige of his specialty Actually it insures a proper co-ordination with the total surgical program, guarantees best that the needs of an advanced training, teaching and an investigative program will be fulfilled, and that extreme specialization and compartmentation will be prevented ", or "I believe all surgical subspecialties should be under the control of general surgery We must recognize that some specialty fields, of which I believe urology is one, have special problems which can never be understood without a thorough general surgical background ", or "The urologic service should have a chief who directs the activities of the service, and the service should be intimately associated with the general surgical program The urologic chief should be responsible to and serve under the jurisdiction of the chairman of the department of general surgery ", and as one man wisely said "So, with most discussions of this type, it is very difficult to plot a course or organizational decisions If you get the right individual it will go well no matter what the administrative set up is and the wrong person will fail in any case The more I think of such problems, the more convinced I am that the solution is the person "

As I have read the letters of these very distinguished surgeons, I have become convinced that their opinions were based on high motives and regard for the welfare of their hospitals and medical schools rather than as an expression of jealous or selfish interests In fact there were only three out of 22 who appeared vindictive or antagonistic in their attitude toward urology One might conclude therefore, that any system of organization relative to urology and general surgery could function well, provided both the urologist and general surgeon were capable and understanding and that neither was obstinate or of a dictatorial disposition

We come now to the opinions of our surgical friends as they pertain to the training of men who will follow us in the urological field Should the training be the same for all those who wish to be urologists? One opinion can be found in the following quote, "We have two types of people to train in this country those who teach and do research, and those who practice " This opinion does not infer that the training of either type should be inadequate, but it does emphasize a concept that perhaps more than one specific or rigid training program might be desirable, depending on the ultimate goal of the prospective urologist

Most of our present discussion will be devoted to the over-all training program As one well-known professor of surgery expressed himself "I think that if one surveyed the field of urology over the country one could criticize a great many urologists because of the narrowness of their outlook, that is, many of them are interested in techniques The way to correct this situation is to urge them to broaden the base of training and insist upon a training in the whole field of surgery as a preliminary to the special training in urology " Similar points of view are expressed by "The urologist should have an adequate training in general surgery before he becomes a surgical specialist " and by "If the properly and basically trained surgeons are to be attracted into this specialty and if the continuing and revivifying inflow of basic medical and surgical knowledge is to be assured, it is necessary to maintain a training program closely related to that of the parent discipline, general surgery This objective can be realized if each surgical internship and assistant residency program contains a proper experience in urological wards and clinics In our opinion, this is not less than one month at the internship level, and three months in a two or three year assistant residency The urological resident should be chosen from the latter group in which case two qualifying years of urology residency would be mandatory, or preferably after a year of general surgical senior residency in which case one year of urology should suffice ", or "This program should be two years for residents who have already had three years of general surgical training " or "Future urologists should have the benefit of from two to three years training in general surgery plus, perhaps, two years of sub-specialty training in urology ", or "I think that urology is very definitely a specialty but I do think that those who enter it should have a good training in the general field of surgery before they limit their activities to the genito-urinary tract " and finally "It is predicted that at least some of the outstanding urologists will oppose the program of which they themselves are a product "

A summary of the opinions of our outstanding surgical colleagues is to the effect that the best training for urologists should include considerable experience in general surgery prior to a two-year period devoted exclusively to urological techniques A similar line of reasoning would no doubt apply to any of the surgical specialties

In the letters upon which this paper is based we have, I believe, specific comment about our specialty which should be taken seriously I have high regard for the individuals quoted and know from the nature of their letters to one of their surgical friends that they were expressing their real thoughts about the inquiry at hand

There is no doubt that urology has developed into a well defined specialty It is probable that this development and maturity has been brought about by 1) the skilled use of special instruments and operative techniques, 2) close attention to both the medical and surgical conditions or diseases of organs in our realm, 3) detailed estimate of the patient prior to any surgical procedure and 4) significant research, both basic and clinical, in our own and other departments of medicine and surgery If these features have been responsible for the development of urology, let us continue to pursue the same principles to safeguard the future

Concerning the organizational set-up in hospitals and medical schools, it appears advisable for urology to have adequate autonomy in the care of patients and provision for research, but that this can be accomplished as a subdivision of general surgery, provided the individuals involved have mutually high principles, are personally compatible, and have confidence in each other

In regard to training, it is evident that the surgical intern and assistant resident should have transient experience in urology as part of their training in general surgery Knowledge of the common urological disabilities in men and women, and of the urological modalities for diagnosis and treatment appear necessary for anyone with a modern background in medicine and surgery

It may be important too, for those who wish to become urologists, not to limit themselves to urological training until they have had considerable experience in the wider field of general surgery This would not necessarily prolong the total period of training if some flexibility were permitted between the years spent in general surgery and urology during the residency program Our friends in general surgery, perhaps surprisingly to us, seem to agree that a two-year period of intensive effort in urology would provide a qualifying experience No doubt many of the outstanding urologists of today had training of this type If one is to avoid the criticism of narrowness in point of view leveled at urology, we might well consider a broader background in surgery and a somewhat shorter period of training in the specialty itself We who are intensely interested in our own specialty can often find wise counsel from those outside our own field Let us give some thought to urology—as others see it

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SCISSION OF UROLOGY—CENOTAPH TO A SUBTLE OFFENSE

CHARLES MONTGOMERY STEWART

Around the turn of this century medical specialties were almost non-existent One of the first and largest clinical specialties was entirely concerned with the diagnosis and treatment of the diseases of venery

Professors of surgery of this era were primarily interested in the non-venereal diseases of the genito-urinary tract The science of urology did not emerge full-grown as did Minerva from the head of Jupiter It slowly developed from a painstaking union and evolution of the venereal and non-venereal disturbances of the urinary and genital systems Urology, as we recognize it today, was guided to its position of eminence by the headwork and handcraftiness of many gifted non-conformists

These were the teacher-explorers imbued with a fanatic faith in their abilities to reach and solve the mysteries confronting them on this new but distant medical horizon Of necessity, they had to be a specialized breed of very specialized individualism To these self-led pioneers the credit must be given for the accumulation of the initial accurate information regarding the anatomy, physiology, pathology and embryology of the genito-urinary tract Urology became an outstanding specialty only because of the pioneer individualism of these many dedicated, though sometimes acrimonious, teacher-leader nonconformists

In the early days urology was assumed to be a division or sub-department of general surgery Gradually it achieved a completely independent status as a separate department in many outstanding medical schools Recently this departmental independence of urology as a diagnostic and surgical specialty has been slowly disintegrating At present a few teaching institutions recognize urology only as a diagnostic specialty The surgical section of urology is being subjected to amputation The men who introduced the original techniques of urogenital surgery, who developed the innovations, eliminated the imperfections and then made these advances known to all branches of medicine are now confounded with the bitter realization that they continue to be recognized for their diagnostic capabilities but surgically they have suddenly been found wanting

Infinity marked the boundaries in all directions of general surgery's operating latitude previous to the introduction of antibiotic and chemotherapy. The advent of orthopedics, chest, cardiac, vascular, proctology, hand and maxillofacial specialties have further decreased the original limitless confines to an area of maneuver which by comparison scarcely provides elbow room However, general surgery's pragmatism has not developed opportunistic myopia as a result of this constant pressure of progress No longer sovereigns of all their scalpels could scan, these argus-eyed autocrats began to cast a covetous nimble optic over the quiet grazing grounds of the neighborhood specialties

As urologists, we must heed the fact that until recently the teaching and practice of urology enjoyed a deserved and respected recognition unsurpassed by any branch of medical endeavor But now in our teaching capacities we practically always accept a decreed classification as a minor division of a major surgical specialty Should we persist in our bland acceptance of this low pedagogic rating? If this abject persistence prevails it is obvious that our general recognition as major specialists must regress from a deserved top to an undeserved bottom level of specialized medical effort

Should we remain in our ignominious positions, kneeling as we steady the bottom of the ladder for the specialist's group who maintain that they alone deserve to occupy the top? Voicing no objection confirms that we conform In conforming, we accept as final the mandate rendered as the ultimate in design for the teaching and practice of urology by these coutouriers of collective-effort medical patterns Our pattern has been cut and is not subject to alteration of even minor degree The design is final It has been planned with care to fit us all and all of us must fit it Changes in castings, moulds and dies of urologic practice patterns will never be wrought by conformists

Originality and conformity cannot co-exist Individualists and craftsmen all suffer the taint of originality Creative craftsmanship requires independence, untamed unconformed individualism Because non-conformists lack numbers, are in evident minority, must they automatically be qualified as odd-balls?

Capitulation is the commonest complication of the present-day general conformity epidemic Capitulate and group-adjustment becomes an instinct Be enthusiastic but completely agreeable and bend to the will of the group Dissatisfaction is a birthmark of the perfectionist, the craftsman, the non-conformed individualist Disagreement will impede smooth group-effort and dictated team play Continual total agreement is the only pattern of behavior accepted as normal in anyone who plans to maintain a place in the new pedagogic pattern

Discourage the man with the dubious or inquiring mind, this attitude is hostile to collective organizational group effort Frown on the individual instinctively driven to develop his God-given talents and latent genius Condemn those unfortunates who uncontrollably generate the compelling excess energy they must expend in extra effort We are all obligated to bolster the bumble-bum We owe the nonentity the right to achieve a sense of significance as a result of our group-guided efforts

Suppression, oppression and pressured direction by the organization or the institution will reduce the urge of creative man to the sterile stature of the dictum-dominated groups, the sum of whose combined original efforts barely qualify them at the level of medicine's mental geldheads

The urinary tract contains no teeth This may justify our edentulous gum-bared whimpers of abjection faintly heard arising from our assigned position at the bottom of the surgical specialties totem pole Our dictated choice of position on the S S Totem Pole is either 1) where the pole enters the ground, or 2) where the pole emerges from the ground We have been graciously granted permission to make a free, uninhibited choice of either of these locations This broad range of latitude might be generously termed limited and it could further support our sneaking impression that our delegated authority has even narrower limitations

These tartufish purveyors of surgery's subtle system of classified caste categories have pushed their offensive into our territory no faster than our timorous withdrawal tactics have permitted. Though our retreat has been slow, nevertheless it has been steady and each urologic retrograde step has been promptly matched, forward for backward stride, as we blissfully fade deeper into our shrinking domain. Our "division" of surgery could disappear entirely should any further "head shrinking" by "shrunken heads" prevail.

Urology discovered and cleared many fruitful diagnostic and surgical pathways. Urologists pioneered and attained many memorable pinnacles in envisioning and perfecting techniques and instruments which have achieved a degree of diagnostic accuracy unrivaled by any other medical or surgical specialty. The visual instruments, electro-surgical units, and various contrast media have provided the basis for countless advances in diagnostic methods and have suggested new uses for variations of our basic instruments. These have now been adapted and adopted for use in the other specialized branches of surgery and medicine.

Individualists have been responsible for the discoveries and developments that have resulted from the painfully slow, probing processes always necessary to maintain stable, sound, constant urological progress.

Creative craftsmanship is an attribute singularly peculiar to the independent, unconformed individualist. His eternal, inborn, impelling curiosity will be hindered, discouraged and finally smothered by exposure to the pressures of institutional integrated group effort. The creator of the basic premise, the conceptor and proponent of revolutionary theory and practice, though often at wide variance with the old and accepted methods, has been, is now and will always be an individualist. He agrees and conforms only in conceding that the application of basic observations, and the proving and adaptation of the individualist's theories are tasks for the organized group and their unified, purposeful, integrated efforts.

Now, who cares? Why object? What good will resistance accomplish? Why should we make anyone mad? We can't reverse the direction of things unless we become disagreeable. Should we keep our heads in the sand and continue to pretend that what we can't see or won't see can't hurt us? Must we continue to plummet from the heights we once attained to join at a common level of assignation with our confréres as they struggle up from the depths? Joined, we may altogether and forever wallow in the serene sea of menial medical mediocrity. Must our pedagogic cataracts be permanent? Have all the old fighting, seeing-eye urological guide dogs become extinct? Can we not seek and find a bold steady hand capable of giving us direct, determined guidance back up the ladder to the deserved level we occupied previously?

Scission, fragmentation, trituration and obliteration constitute a chain reaction that is difficult to halt early and impossible to stop later. Amiel has said, "In every union there is a mystery,—a certain invisible bond which must not be disturbed." Our survival depends on our early prevention of the fission of this bond. Continuation of our shameful, shamanistic acceptance of the strategic retreat as a protective weapon is rank madness.

Urology's original principles, aims and objectives have not varied since they were initially declared Their existence has become obscured by the dense smoke of our abandoned pedagogic and practice bastions ignited by the burning shame of our continued "turn and run without a fight policy "

There is still time to halt, face about and stand firm with a united singleness of purpose and action We must loudly proclaim the resuscitation of our principles, aims and objectives Be prepared to resist future dictation of our rights and privileges Pressure by a group, groups, organizations or institutions must be promptly met by greater counter-pressure or we can abandon all hope of preventing our scheduled docile demise

We should recommend that our local, sectional and national organizations re-issue and re-declare our original declaration of rights policies

Our re-grouping and re-union must present an impenetrable, solid front or our new offense will become merely offensive and will be as potentially disastrous as is our present strategic retreat policy

Scission, fragmentation, trituration and obliteration This could be urology's cenotaph

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SOME METABOLIC ASPECTS OF URINARY CALCULI

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For two decades it has been good practice to look for primary hyperparathyroidism among patients with calcium urolithiasis or nephrocalcinosis. As predicted by Albright and associates, a diligent search for this condition is rewarding in about 5 per cent of cases, and continued screening of urologic patients for hyperparathyroidism has led through the years to recognition of other conditions associated with excessive urinary calcium which, like hyperparathyroidism, may provoke formation of urinary calculi or nephrocalcinosis on occasion. Some of these conditions may be lethal, of themselves, such as multiple myeloma, whereas others, while serious, are amenable to therapy, such as renal tubular acidosis. As is the case with hyperparathyroidism, recognition and treatment of such disorders occasionally provide the urologist with a useful opportunity of putting a halt to the stone-forming process. Unfortunately, only a minority of stone-formers fall in such categories, and the majority of stone-forming patients show no clear-cut abnormality of calcium metabolism of practical clinical significance even after exhaustive and expensive search. Nevertheless, the possibility of decisive aid is real enough to justify some metabolic evaluation of all patients who form stones, and exhaustive metabolic evaluation of many, particularly those with recurrent or multiple stones. Such an evaluation has as its first stage the recognition or exclusion of primary hyperparathyroidism, as its second, the differentiation of other hypercalcemias, and as its third, evaluation of renal hypercalciurias.

LABORATORY AIDS

All these diagnostic problems share a common difficulty, namely, complete dependence of the physician on the laboratory. Hyperparathyroidism could be defined in one view as hypercalcemia for which alternative explanations have been excluded. The other conditions to be discussed may also be discovered at times only through accurate evaluation of reliable laboratory data, rather than discriminating appraisal of clinical history and physical signs. It is appropriate therefore to discuss certain laboratory procedures briefly.

Serum calcium. Values cited in many texts for the normal range of serum calcium are usually 9 to 11 mg. per 100 ml. (or even 8 to 12). Such ranges are misleading and may reflect older methods, at any rate they are not sufficiently precise for present application. The mean value for serum calcium in 109 healthy adults in our laboratory was 9.77 mg. per 100 ml.* with a standard deviation of 0.31 mg. per 100 ml. The "normal range" including 95 per cent of the normal population so described is 9.2 to 10.4 mg. per 100 ml. The error of the method as indicated by replication is 0.01 mg. per 100 ml.

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* By the method of Power, Toogood and Adamson, employing oxalate precipitation and permanganate titration.

Read at annual meeting of American Association of Genito-Urinary Surgeons, Hot Springs, Va., May 1-3, 1957.

Serum phosphorus Serum inorganic phosphorus in 109 adults averaged 3 4 mg per 100 ml * and the "normal range" encompassing 95 per cent of an adult population was 2 5 to 4 3 mg per 100 ml It should be noted that a fourth of the normal population by this method have serum phosphorus values in the range 2 5 to 3 0 mg per 100 ml , commonly accepted as below normal

CONDITIONS IN WHICH CALCULI ARE FORMED

Calciuria Urinary excretion of calcium must be evaluated with the patient on a diet in which the calcium intake is known and controlled We have employed a quantitative diet containing 2,000 calories and 135 mg of calcium per day (the "Bauer-Aub diet"), usually for 3 days at a time Normal persons usually excrete less than 100 mg of calcium per day on this program Some healthy individuals may excrete up to 150 mg per day, but values in excess of this figure may be regarded as abnormally elevated

Primary hyperparathyroidism Primary hyperparathyroidism must be distinguished from other conditions associated with hypercalcemia hypervitaminosis *D*, multiple myeloma, *Boeck's* sarcoid, carcinomatosis ossei (and also carcinomatosis without obvious skeletal involvement in certain instances), acute osteoporosis of disuse, Paget's disease with immobilization, and the milk-alkali syndrome, all of which may produce renal calculi or nephrocalcinosis Primary hyperparathyroidism shares with *these conditions a group of symptoms associated* with hypercalcemia per se These are muscular weakness, fatigue, polyuria and polydipsia, and gastrointestinal symptoms such as constipation, anorexia, epigastric pain, and nausea and vomiting The serum calcium must usually be *substantially* elevated (that is, more than 12 mg per 100 ml) before such symptoms are encountered

If significant osseous disease is present, patients with hyperparathyroidism may have symptoms referable to the skeleton These may include all manner of crippling deformities, pathologic fractures, cysts and tumors of bone, and the like In less severe cases, skeletal symptoms may consist only of vague and ill-defined aches and pains When such osseous symptoms are present, a competent roentgenographic examination should automatically lead to the correct diagnosis Determination of alkaline phosphatase provides both a clue to the presence of bone disease and a measure of its severity but has nothing *directly to do* with parathyroid function The level of alkaline phosphatase may, in fact, be quite normal if the skeleton is not grossly involved, even though severe hyperparathyroidism is present

Hyperparathyroidism may produce symptoms referable to the urinary tract whenever kidney stones or nephrocalcinosis occurs There is widespread belief that there is something pathognomonic or specific about the urinary manifestations of parathyroid disease, but, alas, such is not the case Any and all of the signs and symptoms of kidney stones and their complications and all of the consequences of nephrocalcinosis may occur and, when they do occur, are indistinguishable from the urologic disturbances encountered in patients without parathyroid disease The composition of the kidney stones is not helpful Three fourths of the stones examined from cases of proved hyperparathyroidism are reported to consist predominantly of calcium oxalate, the remainder are calcium carbonate or calcium phosphate Relatively few are branched stones

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* By modification of the method of Fiske, C H , Subbarow, Y and Gomori, G J Lab & Clin Med , 27 955, 1942

Lastly, there is a growing number of patients proved to have hyperparathyroidism despite complete absence of symptoms referable either to urinary tract or skeleton These patients with asymptomatic hyperparathyroidism have usually been found entirely by accident ("serendipity") or as a result of blindly seeking the condition at random in a large group of patients The study of such individuals has led to the concept that hyperparathyroidism is a disease which in its milder forms produces no recognizable signs or symptoms until some complication occurs, such as osteitis fibrosa or nephrolithiasis Prolonged followup of patients with such asymptomatic hyperparathyroidism justifies the conclusion that such complications, especially urolithiasis, are probably certain to occur sooner or later, although one such patient was followed for more than 10 years before urolithiasis developed for the first time

Hypervitaminosis D Hypervitaminosis D may sometimes closely simulate hyperparathyroidism clinically and chemically The general impression that hypophosphatemia does not occur in this condition and, therefore, that the absence of hypophosphatemia differentiates hypervitaminosis D from primary hyperparathyroidism is, unfortunately, not always true While osteitis fibrosa cystica is not seen, some skeletal demineralization and nephrocalcinosis sometimes occur, and calculi have rarely been seen There is no convenient means of differentiating hypervitaminosis D from hyperparathyroidism other than by obtaining a history of ingestion of vitamin D in toxic amounts In some cases treatment with cortisone, or with a diet low in calcium with copious fluids may ameliorate or correct the hypercalcemia in a few days, but in others, the abnormal calcium metabolism may be for a time as refractory to such treatment as is hyperparathyroidism Theoretically, demonstration of decreased fecal excretion of calcium by metabolic balance techniques might prove diagnostically useful, but this is not a clinically practical method

Sarcoidosis This may prove difficult to differentiate from primary hyperparathyroidism Early studies were interpreted as showing that hypercalcemia occurred in this condition, as well as in myeloma, only in association with hyperproteinemia On the contrary, it is now clear that hypercalcemia disproportionate to hyperproteinemia, or even without hyperproteinemia, occurs fairly often in sarcoidosis Serum phosphorus may be reduced at times and this, in association with renal lithiasis or nephrocalcinosis, may in some instances make sarcoid exceedingly difficult to differentiate from primary hyperparathyroidism The finding of an elevated sedimentation rate should initiate further study, while lymphadenopathy or cutaneous or pulmonary disease has on occasion provided diagnostic information decisive enough to avoid unnecessary exploration for parathyroid disease

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The disturbance of calcium metabolism producing hypercalcemia and its consequences in sarcoid disease appears to be the result of an endogenous hypervitaminosis D and, like exogenous hypervitaminosis D, may occasionally be differentiated from hyperparathyroidism by a therapeutic trial of adrenal steroids or of a diet low in calcium with copious fluids There is uncertainty whether the lesion of sarcoidosis produces a substance physiologically similar to vitamin D or one which potentiates the action of vitamin D and thus sensitizes the patient to normal quantities of vitamin D Whichever is the case, the essential metabolic changes in this disease are analogous to those of hypervitaminosis D, namely, increased gastrointestinal absorption and reduced fecal excretion of dietary calcium

Multiple myeloma Like sarcoidosis, this may sometimes be characterized by hypercalcemia, hypophosphatemia, and hypercalciuria, as well as by skeletal lesions and urolithiasis Whereas an elevated sedimentation rate, characteristic roentgenographic findings, and the demonstration of myeloma cells on sternal aspiration may differentiate the conditions, myeloma may sometimes simulate hyperfunctioning parathyroid disease closely indeed

Carcinomatosis ossei Extensive skeletal destruction by malignant cells sometimes results in precisely the same pattern of hypercalcemia described for sarcoid or myeloma Some recent work would indicate that hypercalcemia may occasionally occur in association with disseminated carcinomatosis even though the skeleton is not demonstrably involved The disturbance of calcium metabolism involved in such instances may prove analogous to that described in sarcoid

Acute osteoporosis of disuse Abrupt immobilization of healthy young adults, as by paralysis or serious injury, may produce an acute pattern of massive demineralization of the skeleton, hypercalcemia, hypercalciuria, renal insufficiency, and renal lithiasis While the obvious cause generally precludes diagnostic confusion, it should be noted that the characteristic changes in the composition of blood and urine may be virtually indistinguishable from those occurring in the other hypercalcemic disorders described An analogous situation following immobilization has been described in older persons with extensive polyostotic osteitis deformans (Paget's disease)

Milk-alkali syndrome Renal insufficiency and hypercalcemia (sometimes with normal or even slightly lowered serum inorganic phosphorus) may result from excessive ingestion of milk and absorbable alkali, usually taken as treatment for peptic ulcer The resulting symptoms of hypercalcemia, sometimes with involvement of the urinary tract as well as calcinosis elsewhere, have occasionally caused these patients to be suspected of primary hyperparathyroidism and, in more than one instance, to undergo surgical exploration for parathyroid disease The differential diagnosis, however, is seldom difficult provided a history of gastrointestinal disease and excessive ingestion of milk and absorbable alkali is obtained Hypercalciuria, as defined by the Bauer-Aub test, is absent However, urinary concentration of calcium great enough to contribute to calculus formation may be presumed to occur during ingestion of milk and absorbable alkalies (often calcium salts) but does not persist when excess dietary calcium is withheld In some instances hypercalciuria has been observed the first day of study on a diet low in calcium The diagnosis is further confirmed by demonstrating rapid fall of serum calcium when the patient is given copious fluids and fed a diet low in calcium for a few days Some improvement of hypercalcemia may occasionally occur in similar circumstances in hypervitaminosis D or sarcoidosis but has not been encountered in the other conditions which have been enumerated

In practice most of the foregoing conditions can be distinguished from one another without particular difficulty, despite the common denominator of hypercalcemia In occasional instances, however, the differential diagnosis of the hypercalcemias may be extraordinarily difficult and may tax the skill experience, and resources of the physician to the utmost The same comments may be applied with equal force to the diagnosis of primary hyperparathyroidism per se Ordinarily the diagnosis of this condition is easy once the possibility has been thought of, and several blood determinations have been obtained, the characteristic changes therein supported by definite hypercalciuria are quite decisive Once alternative explanations are excluded, the diagnosis is usually secure Difficulties arise as one attempts to establish the diagnosis in milder cases or in patients with impaired renal function in whom the pathognomonic chemical criteria are likely to be equivocal With progressive renal insufficiency the elevated serum calcium falls, while the serum inorganic phosphate rises proportionately to nitrogen retention

Present experience indicates that the average level of serum calcium need be elevated only a fraction of a milligram above the normal range in some cases, and in perhaps a fourth of the cases one or more determinations may be within the normal range In about a third of the cases the mean value of inorganic phosphate lies between 2 5 and 3 0 mg per 100 ml, which while within the range of normal as defined here, is "low" by ordinary standards In a few instances the mean value of serum phosphorus has been more than 3 0 mg per 100 ml even though no evidence of renal impairment was present' Urinary excretion of calcium may likewise be equivocal in mild cases In general, evaluation of serum calcium and phosphorus and of urinary calcium taken together carries more weight than does any one test alone, particularly when the average of several determinations is used Accurate assessment of such trivial alterations of serum levels is possible only if the laboratory is extraordinarily reliable and the physician is thoroughly conversant with the standards and variations characteristic of the laboratory

The need for diagnostic accuracy is accentuated by the considerable technical complexities of parathyroid surgery The diagnostician must do more than tell his surgical colleague This patient may have parathyroid tumor, probe around a bit and see if you can find one " The exploration for parathyroid tumor is too formidably difficult for a negative exploration to be diagnostically decisive unless four normal glands can be found and identified The surgeon, therefore, requires and deserves reasonable certainty that a hyperfunctioning lesion is present

SPECIAL DIAGNOSTIC TESTS

The foregoing situation has led to the development of three new diagnostic maneuvers for the evaluation of equivocal hypercalcemias These are the calcium-loading test, measurement of the tubular reabsorption of phosphate, and the phosphate deprivation test

The calcium-loading test has been evaluated by Howard and associates It consists of observing the effects on urine phosphorus excretion and serum phosphate of giving a large intravenous load of calcium The patient is given an infusion of 15 to 25 mg of calcium as calcium gluconate per kilogram of body weight over a period of 8 hours The following morning, a normal person will show elevation of serum phosphorus (greater than 0 5 mg per 100 ml) and a reduction of urinary phosphate to one half or one third A patient with hyperparathyroidism generally shows no increase of serum phosphorus and little or no decrease of urinary phosphate In addition to elucidating borderline calcium values, the test is occasionally useful in separating other forms of hypercalcemia from those due to parathyroid disease It is not infallible, and paradoxical results occasionally occur

The tubular reabsorption of phosphate can be estimated in the course of the Bauer-Aub test or the calcium-loading test The serum concentrations and urinary excretion of phosphate and creatinine are determined The endogenous creatinine clearance is taken to be an index of glomerular filtration, and the difference between this and phosphate clearance is assumed to be phosphate reabsorbed Normal persons usually will reabsorb 80 per cent or more of glomerular filtered phosphate, whereas patients with parathyroid disease usually show lower values, sometimes as low as 50 per cent The test is not valid in patients with impaired renal function—a serious objection—but offers another means of sometimes differentiating other hypercalcemias from parathyroid disease where this proves difficult

In the phosphate deprivation test the patient follows a diet which is poor in phosphorus and high in calcium for a week or longer This procedure is said to intensify the pathognomonic sign of hyperparathyroidism if present (by depressing serum phosphate and increasing serum calcium) and to restore equivocal values to normal in those instances in which hyperparathyroidism is not present

TREATMENT

Hypercalcemia Hyperparathyroidism is almost invariably a curable, surgical disease providing its renal consequences have not reached an irreversible and ultimately fatal stage Approximately 80 per cent of cases are due to adenoma In 4 per cent there are multiple adenomas An additional 4 per cent of cases are associated with multiple endocrine adenomatosis in which adenomatous hyperplasia of two or more parathyroids with hyperparathyroidism is associated with an analogous change in the islands of Langerhans and hyperinsulinism, and, in some cases, with pituitary adenomas Nine per cent of cases are associated with hyperplasia of wasserhelle cells and hypertrophy affecting all four parathyroids, while in a very few instances truly malignant tumors, generally adenocarcinomas, have been found

The treatment of hypercalcemia other than hyperparathyroidism is quite varied Myeloma and carcinomatosis are probably not directly amenable to treatment The acute osteoporosis of disuse and the hypercalcemia that results from immobilization in cases with extensive Paget's disease can be combated successfully by mobilization of the patient If no other course is available, this may be achieved by putting the patient on a rocking bed The hypercalcemia of sarcoidosis, hypervitaminosis D, and the milk-alkali syndrome are best treated by a low-calcium diet and liberal fluids This is usually rapidly effective in milk-alkali syndrome and occasionally so in hypervitaminosis D and sarcoidosis The hypercalcemia in sarcoid and hypervitaminosis D may respond favorably to the exhibition of cortisone

Hypercalciuria without hypercalcemia Hypercalciuria may occur without hypercalcemia in milder instances of some of the conditions already enumerated, such as acute osteoporosis, hypervitaminosis D, and perhaps some cases of myeloma or carcinomatosis

In 1939 Flocks noted that the majority of patients with hypercalciuria have normal serum calcium and do not have hyperparathyroidism Most, if not all, of these patients probably have an intrinsic defect of renal tubular function It is of practical value to distinguish at least two categories of such patients for purposes of treatment The first of these includes patients who can be recognized as having what Albright called "tubular insufficiency without glomerular insufficiency" The condition is often termed "hyperchloremic acidosis" because of its most conspicuous chemical characteristics Such a condition may be congenital but is probably sometimes acquired, as a residue of previous pyelonephritis The patients show reduction of serum carbon dioxide-combining power, compensatory increase of serum chloride, an alkaline urine, usually hypercalciuria, and an associated propensity to nephrocalcinosis or renal lithiasis Usually there is also reduced ability to form ammonia, reduced titrable acidity, and increased urinary phosphate In more severe cases, the patient may also have hypokalemia, hypophosphatemia, muscular weakness, and osteomalacia, although, as with primary hyperparathyroidism, many of these features are sometimes lacking Perhaps the most direct clue to the existence of the condition is the coexistence of metabolic acidosis (reduced carbon dioxide-combining power) and an alkaline urine in patients without nitrogen retention When this combination is associated with hypercalciuria, therapy with soluble alkali is usually in order Providing there is no azotemia, treatment with 100 to 150 mEq of sodium bicarbonate per day (supplemented by potassium salts if hypokalemia is present) may often produce a striking response The hypercalciuria, hyperchloremia, hypokalemia, and acidosis may be quickly corrected, and in addition, there is usually improved strength and sense of well-being

Why do patients with tubular acidosis respond in this unusual manner? It is generally considered that their intrinsic renal tubular defect makes it impossible for them to conserve base As a consequence they waste sodium, potassium, and

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In the phosphate deprivation test the patient follows a diet which is poor in phosphorus and high in calcium for a week or longer This procedure is said to intensify the pathognomonic sign of hyperparathyroidism if present (by depressing serum phosphate and increasing serum calcium) and to restore equivocal values to normal in those instances in which hyperparathyroidism is not present

TREATMENT

Hypercalcemia Hyperparathyroidism is almost invariably a curable, surgical disease providing its renal consequences have not reached an irreversible and ultimately fatal stage Approximately 80 per cent of cases are due to adenoma In 4 per cent there are multiple adenomas An additional 4 per cent of cases are associated with multiple endocrine adenomatosis in which adenomatous hyperplasia of two or more parathyroids with hyperparathyroidism is associated with an analogous change in the islands of Langerhans and hyperinsulinism, and, in some cases, with pituitary adenomas Nine per cent of cases are associated with hyperplasia of wasserhelle cells and hypertrophy affecting all four parathyroids, while in a very few instances truly malignant tumors, generally adenocarcinomas, have been found.

The treatment of hypercalcemia other than hyperparathyroidism is quite varied. Myeloma and carcinomatosis are probably not directly amenable to treatment. The acute osteoporosis of disuse and the hypercalcemia that results from immobilization in cases with extensive Paget's disease can be combated successfully by mobilization of the patient. If no other course is available, this may be achieved by putting the patient on a rocking bed. The hypercalcemia of sarcoidosis, hypervitaminosis D, and the milk-alkali syndrome are best treated by a low-calcium diet and liberal fluids. This is usually rapidly effective in milk-alkali syndrome and occasionally so in hypervitaminosis D and sarcoidosis. The hypercalcemia in sarcoid and hypervitaminosis D may respond favorably to the exhibition of cortisone.

Hypercalciuria without hypercalcemia. Hypercalciuria may occur without hypercalcemia in milder instances of some of the conditions already enumerated, such as acute osteoporosis, hypervitaminosis D, and perhaps some cases of myeloma or carcinomatosis.

In 1939 Flocks noted that the majority of patients with hypercalciuria have normal serum calcium and do not have hyperparathyroidism. Most, if not all, of these patients probably have an intrinsic defect of renal tubular function. It is of practical value to distinguish at least two categories of such patients for purposes of treatment. The first of these includes patients who can be recognized as having what Albright called 'tubular insufficiency without glomerular insufficiency.' The condition is often termed 'hyperchloremic acidosis' because of its most conspicuous chemical characteristics. Such a condition may be congenital but is probably sometimes acquired, as a residue of previous pyelonephritis. The patients show reduction of serum carbon dioxide-combining power, compensatory increase of serum chloride, an alkaline urine, usually hypercalciuria and an associated propensity to nephrocalcinosis or renal lithiasis. Usually there is also reduced ability to form ammonia, reduced titrable acidity, and increased urinary phosphate. In more severe cases, the patient may also have hypokalemia, hypophosphatemia, muscular weakness, and osteomalacia, although, as with primary hyperparathyroidism, many of these features are sometimes lacking. Perhaps the most direct clue to the existence of the condition is the coexistence of metabolic acidosis (reduced carbon dioxide-combining power) and an alkaline urine in patients without nitrogen retention. When this combination is associated with hypercalciuria, therapy with soluble alkali is usually in order. Providing there is no azotemia, treatment with 100 to 150 mEq of sodium bicarbonate per day (supplemented by potassium salts if hypokalemia is present) may often produce a striking response. The hypercalciuria, hyperchloremia, hypokalemia, and acidosis may be quickly corrected, and in addition, there is usually improved strength and sense of well-being.

Why do patients with tubular acidosis respond in this unusual manner? It is generally considered that their intrinsic renal tubular defect makes it impossible for them to conserve base. As a consequence they waste sodium, potassium, and calcium and, for some reason, relatively more calcium than other cations, hence hypercalciuria results Liberal administration of sodium and in some instances potassium also permits the kidneys to spare calcium and to excrete preferentially the soluble cations

When one considers this condition in the presence of borderline laboratory findings it may be difficult to be sure where physiologic variations leave off and significant hyperchloremic acidosis begins Accordingly alkali therapy is often tried in patients with equivocal changes in serum chlorides and carbon dioxide-combining power and an unproved diagnosis (some of whom will have the disease and some will not) If a significant tubular defect is present the patient will usually show a striking clinical response and tolerate bicarbonate very well, whereas another patient with equivocal chemical data, but without tubular insufficiency, will seldom tolerate bicarbonate in the dose prescribed more than a week or two and will not show decisive response in blood levels A therapeutic trial, therefore, has some diagnostic significance in borderline cases

Several other varieties of tubular insufficiency have been described, each with characteristic physiologic defects, including amino-aciduria, glycosuria, and other changes While all of them show excessive urinary excretion of phosphorus ("phosphate diabetes") and a tendency toward osteomalacia, most differ from the syndrome here discussed in not producing hypercalciuria or urolithiasis, although there are several varieties such as the Fanconi syndrome and related conditions which may do so

Idiopathic hypercalciuria There remain a large number of patients with hypercalciuria who are found to have normal serum calcium and no disturbance of serum chlorides or bicarbonate In some of these patients hypophosphatemia is also observed For want of a better term, such cases are categorized as "idiopathic hypercalciuria," a category probably comprising more than one pathologic entity The etiologic and therapeutic significance of idiopathic hypercalciuria was emphasized many years ago by Flocks it may cause kidney stones just as surely as hyperparathyroidism and, unfortunately, is sometimes more difficult to treat It is in this group of cases particularly that various metabolic maneuvers are currently being evaluated, such as administration of phytate and aluminum gels Aluminum carbonate therapy ("the Shorr regimen") is difficult and hence is usually restricted to patients with much at stake and sufficient motivation for a rigorous program It consists of an attempt to reduce ingestion of phosphorus to a point at which urinary phosphate is as low as possible, thus facilitating solubility of calcium salts in the urine In addition to a very Spartan diet low in phosphorus, the patient is given large doses of aluminum carbonate following meals This material combines with dietary phosphate to form aluminum phosphate, which is excreted unabsorbed in the feces Fortunately, it appears that relatively few patients actually need to follow the Shorr regimen and fewer still are willing to do so for prolonged periods, in those who do, results are often gratifying A diet low in phosphorus should theoretically eventually result in osteomalacia, and we have encountered this in one instance

There is currently much interest in the use of phytate (sodium inositol hexaphosphate) for the treatment of hypercalcemia and hypercalciuria of various types. This material prevents absorption of dietary calcium from the bowel in a manner analogous to that by which aluminum carbonate prevents absorption of phosphate; that is, it permits formation of insoluble calcium salts. Phytate therapy is thus a means of severely curtailing dietary calcium. While it will almost completely eliminate calcium absorption and thus greatly reduce calciuria, it unfortunately increases phosphorus absorption and, consequently, phosphaturia for the reason that phytate is composed largely of phosphorus. The net effect on the urinary solubility of calcium may therefore possibly not always be to the patient's advantage.

A METABOLIC SURVEY

From the foregoing considerations it is possible to evolve a working program for evaluating metabolic factors in patients with kidney stones or nephrocalcinosis. How thoroughly such a program should be pursued in an individual case must at times be determined in part by consideration of how much the patient has at stake. A patient who has a single stone and two good kidneys may, of course, never have another episode. We believe that even such patients should be investigated at least to the extent of excluding primary hyperparathyroidism, but the physician may not always feel justified in involving such a patient in a more time-consuming and expensive program. However, the patient with repeated renal colics, multiple stones, repeated renal surgery, or damaged kidneys should be, and usually is, willing and deserving of every therapeutic and diagnostic aid available.

Thorough study usually involves several estimations of serum calcium and phosphorus and an estimation of alkaline phosphatase to evaluate the need for a skeletal survey. Quantitative evaluation of calciuria is usually important. Special tests, such as the calcium-loading test, calculation of phosphate reabsorption, and the like, are usually reserved for the difficult diagnostic problems. Ruling out various sources of hypercalcemia, once this is demonstrated, can involve a very comprehensive examination. In the absence of hypercalcemia or azotemia, estimation of serum electrolytes (sodium, potassium, carbon dioxide-combining power, chlorides) provides a basis for considering tubular disease. When equivocal data appear, repeated chemical analyses and protracted observation may be unavoidable.

The foregoing diagnostic plan has one serious shortcoming: it is very easy for both patient and physician to become too hopeful of the likelihood of success. It must be emphasized that such metabolic surveys of patients who have stone will produce a few triumphs but only at the cost of many disappointments. The proportion of patients in whom positive findings of decisive therapeutic significance will be found is, and probably will remain, a distinct minority.

SUMMARY

Many conditions may contribute to the production of renal calculi or nephrocalcinosis by causing hypercalciuria. Some of these are accompanied by hypercalcemia as well as hypercalciuria primary hyperparathyroidism, hypervitaminosis D, sarcoidosis, multiple myeloma, carcinomatosis, acute osteoporosis, and Paget's disease with immobilization In other conditions hypercalciuria may occur with normal serum calcium, as in tubular insufficiency without glomerular insufficiency (hyperchloremic acidosis) and idiopathic hypercalciuria Careful metabolic survey of patients with renal lithiasis will disclose a few with a significant systemic malady and a significant number who may be decisively helped by discovery of a specific cause amenable to treatment

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HYDRONEPHROSIS PLASTIC SURGERY OF URETEROPELVIC JUNCTION ANALYSIS OF 36 SURGICAL CASES

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The term, hydronephrosis, created by Rayer, has been in use more than one hundred years We accept the term as one relating to ischemic secondary atrophy of the kidney parenchyma due to urinary obstruction of any kind and located in any portion of the urinary tract

A great amount of work has been done in this field We must chiefly recall contributions made during the last 30 years by Hinman, Peter, Hinman and Lee Brown, Hinman and Redewill and by Fuchs These outstanding works should be studied by all who need a better understanding of the subject

As we are interested now only in surgical repair of hydronephrosis, chiefly at the ureteropelvic junction, we need to call attention to the tremendous literature on this particular subject Numerous procedures have been proposed Almost all urologists have their own technique We shall only mention the landmarks in the literature Trendelenburg and Albarran have worked on the subject We need also to refer to Peck, who stressed the importance of abnormal blood vessels in the blockage of urinary drainage He advised the need of section of the ureter and its reimplantation in the pelvis in those cases in which the blood vessels were voluminous Jewett's work likewise is to be recalled, which is a study of the importance of blood vessels (24 out 71 cases) in which there was also intrinsic obstruction of the ureteropelvic junction Fenger and also Schwyzer have developed the technique of longitudinal incision of the obstructed area and a transverse suture These methods were improved by Foley with his world-wide known procedure The Henline-Gentile procedure which we have used many times is a slight modification of Foley's method

Many authors have reported techniques, as their own, not knowing that the methods have been already published The same was about to happen to me but when I started to search the literature I found that Young had already published the identical technique in 1932 We must finally mention the important improvements made by Davis, Culp, Deming, Östling, Hellström and associates, Schlumberger and Riparetti and the very recent report of Jameson and associates, in regard to treatment of hydronephrotic intrarenal pelvis

I wish to present an analysis of the cases upon which we have operated in our urological clinic in the São Paulo University, Brazil

MATERIAL

We have studied 36 cases of noncalculous obstructions of the ureteropelvic junction in which we have performed conservative surgical procedures All were operated upon by ourselves or members of our staff (assistants and chief residents)

Accepted for publication June 13 1957

The oldest case studied has been observed for 8 years, the newest, 7 months Twenty-two cases have been followed, 14 have not been followed

The most frequent *age* was between 30–40 years (14 cases) Between 10–30 we found 12 cases and from 40–70, 10 cases

Twenty-four patients were women and 12 men

The most common *clinical feature* which we have found was the kidney pain reflected pain, 9 cases, unreflected pain on the back, 20 cases, bilateral pain, 5 cases, palpable tumor, 2 cases, pyuria, 4 cases, hematuria, 3 cases, tenderness, 1 case, anuria, 1 case

Often the principal symptoms were associated, but the most common feature was nonreflected pain in the diseased side

Study of the *opposite kidney* disclosed hydronephrosis, 2 cases, stones, 5 cases, accidental suture (hysterectomy), 1 case, pyonephrosis, 2 cases, blockage by stone, 1 case, hypoplastic kidney, 1 case, healthy kidney, 24 cases

Etiology was as follows abnormal blood vessels, 19 cases, "éperon" inside the pelvis, 1 case, nephroptosis plus kinks and/or fixed bands, 5 cases, stenosis of upper ureter, 2 cases, stenosis of middle ureter (retrocaval), 1 case, intrinsic stricture of pyeloureteral junction, 2 cases, extrinsic bands of ureteropelvic juncture, 5 cases, anomalies (kidney and/or ureter), 2 cases, hydronephrosis plus kidney cyst, 1 case, redundant pelvis to be resected, 21 cases

The surgical procedures were Henline-Gentile technique, 19 cases, Ormond Culp, 1 case, Foley, 1 case, Fenger, 2 cases, nephropexy plus resection of bands, 5 cases, resection of aberrant vessels, 17 cases, transposition of huge vessels (Young), 2 cases, T-tube, 4 cases, nephrostomy, 21 cases, splinting (polyethylene), 25 cases, resection of ureter plus anastomosis (end-to-end), 1 case

COMMENTS

One who is going to operate upon a case of hydronephrosis needs to be able to perform all of the known procedures and, sometimes, must be able to devise a technique appropriate to the particular case Certain principles must be kept in mind

1) Besides perfect nephroureterolysis, we must know the condition of the interior of a hydronephrotic sac, especially the permeability of the ureteropelvic junction after dissection, 2) be sure of the area irrigated by an obstructive blood vessel (compressing it and looking for the ischemic area), 3) determine if there is not another cause of obstruction by passing a catheter down the ureter

Sometimes only pyeloureterolysis resolves the question, chiefly in the absence of associated obstruction (intrinsic stenosis sometimes associated with blood vessels) After the lysis, if the pelvis continues as large as before, we need to open and explore it before doing a resection provided that the pelvis is extrarenal For the intrarenal pelvis, we now have the Jameson procedure If this latter technique proves to be as useful as Jameson believes, we shall be able to resolve a difficult problem

As far as blood vessels are concerned, there is no agreement among authors, the majority avoid cutting them as much as possible, like Papin, Jewett, Young,

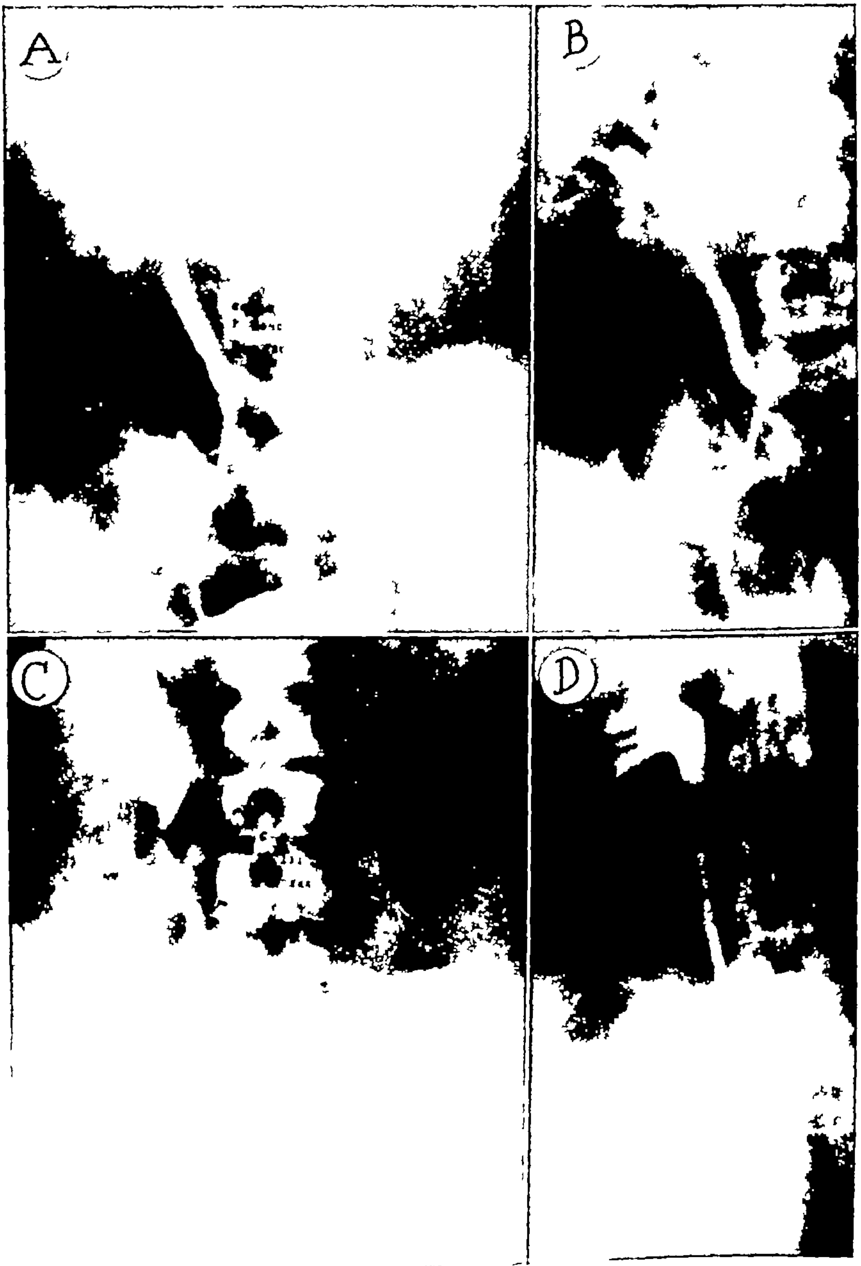

Fig 1 *A* and *B*, case 2 *A*, preoperative retrograde pyelogram Right pyeloplasty and, later, left nephrectomy *B*, postoperative retrograde pyelogram *C* and *D* case 7 *C*, preoperative and *D*, postoperative pyelogram Good function on right side Slight dilatation

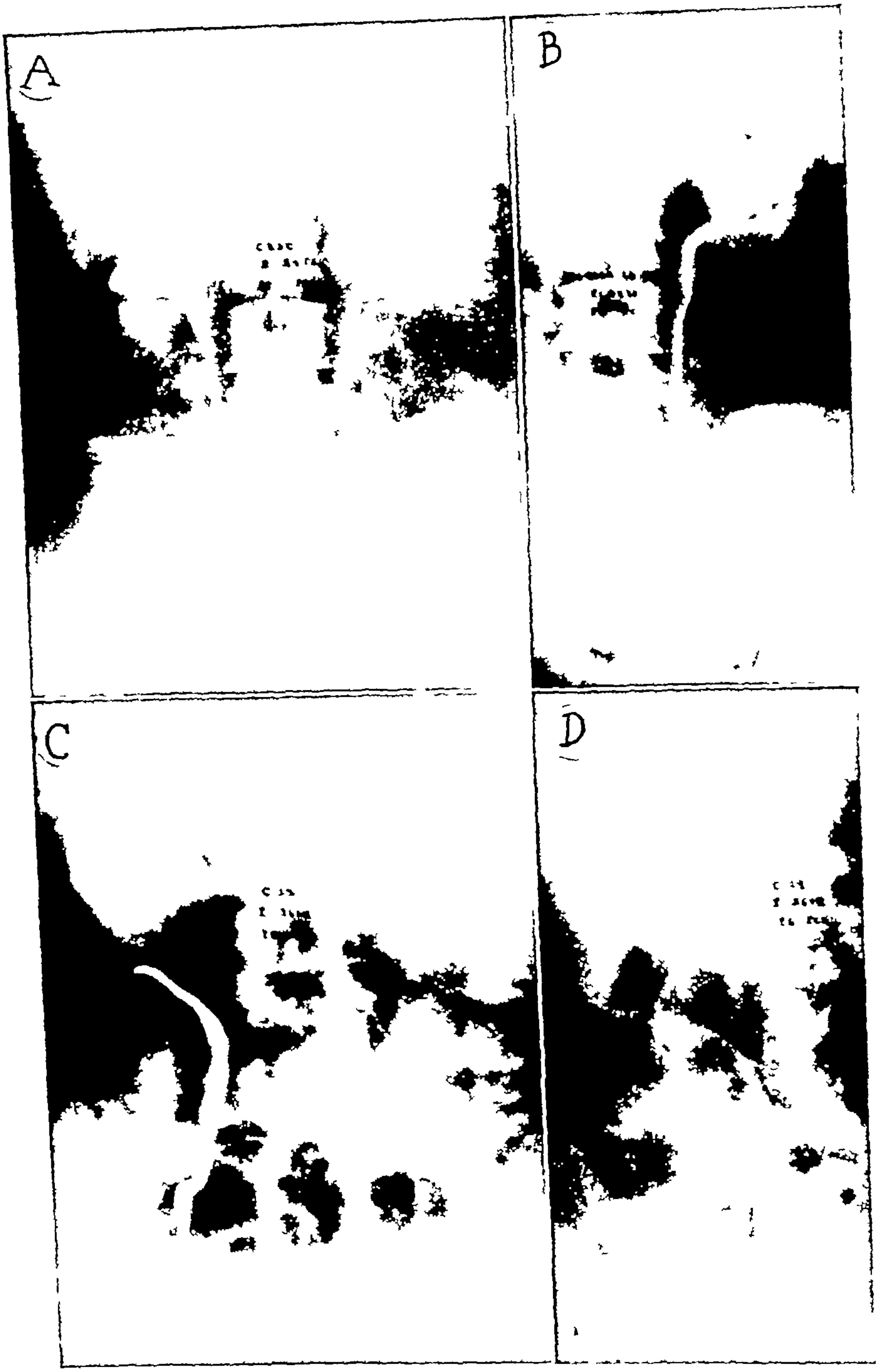

FIG 2 A and *B* case 13 *A* preoperative retrograde pyelogram Huge hydronephrosis *B*, postoperative pyelogram Good result

C and *D* case 14 *C* preoperative retrograde pyelogram Huge right hydronephrosis and tremendous calculus on left Culp s technique used on right side *D* postoperative retrograde pyelogram Good morphological results Intravenous urography disclosed good function Later left nephrectomy was performed

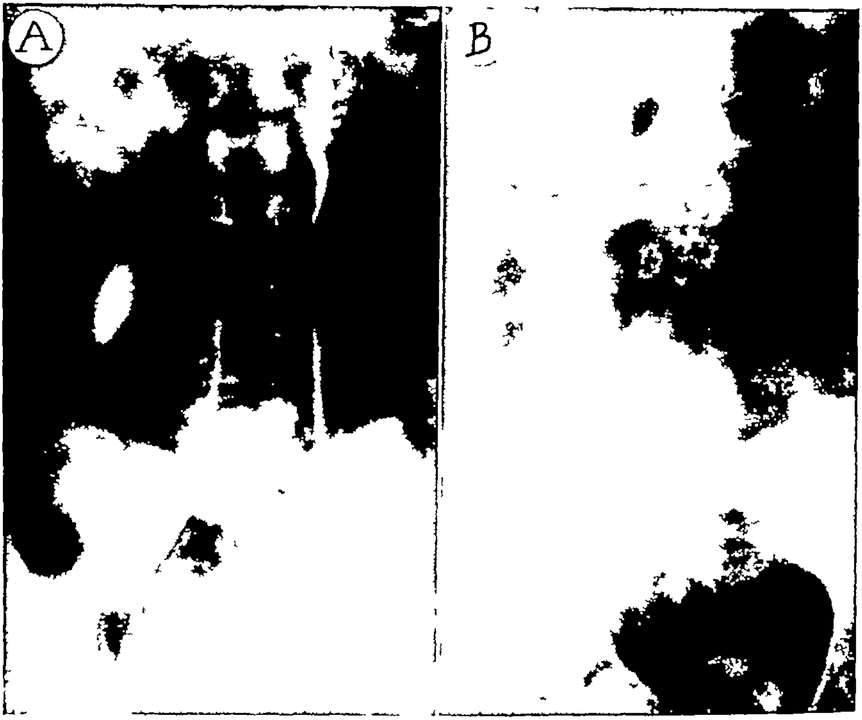

FIG 3 Case 16 A, preoperative retrograde pyelogram Right retrocaval ureter plus hydronephrosis Hydroplastic kidney on left B, postoperative retrograde pyelogram Slight dilatation of upper ureter Tests and intravenous urography revealed good function on right side Left kidney functionless

and others We prefer to preserve them as much as it is possible when they are big Some others, like Kummell and Mathé, say that section of the vessels may be done without danger, when less than a third of kidney is irrigated by them We don't favor this position because an ischemic area may be followed by infarction, postoperative bleeding and loss of kidney function with all its consequences

For nephropexy, we recommend the Deming procedure which proved to be quite satisfactory in our hands

We are not quite sure how long splints must remain in place In our cases we have left them for 3 weeks at least We have used both T-tube and polyethylene for splints Regardless of some advantages that T-tubes afford for drainage and splinting, they are prone to incrustation and come out easily We prefer to use polyethylene or polyvinyl

Our results were *good* in 19 cases (52 77 per cent), regular in 8 (22 20 per cent) not improved in 2 (5 55 per cent) and poor in 7 (19 48 per cent) But if we consider as good those cases in which the kidney function recovered and the patients are free of symptoms, we can say that 27 cases (74 97 per cent) have been benefited by the operation Illustrative cases have been depicted in figures 1, 2 and 3

Poor results were obtained in 7 cases Cases 8 and 34, the operative procedure was unsatisfactory, case 10, kidney function did not return case 11, stone was left behind, cases 19 and 29, a pyelocutaneous fistula developed, case 25 the hydronephrotic sac became larger

In such cases we need to perform a secondary nephrectomy We are happy however to have tried conservative surgery so often because we have thereby saved many kidneys

We have had no deaths in our series, we believe that our judgment was sound and we shall continue thusly

SUMMARY

The author has reported his experience in 36 surgical cases of hydronephrosis due to obstruction at the ureteropelvic junction, during the period 1948–1957

In the author's opinion, the surgical procedure of choice depends upon the nature of the obstruction rather than personal preference of the surgeon

The author has performed many types of operation in these cases He favors resection of the pelvis in those cases in which the redundancy justifies the procedure He emphasizes the value of Henline's technique in such instances He does not like the T-tube and prefers a nephrostomy tube and polyethylene splinting His results are analyzed with emphasis on the unsatisfactory ones (7 cases, 19 48 per cent) In some cases in spite of return of renal function, the pelvis remained enlarged No deaths occurred in the series

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ANEURYSM OF THE RENAL ARTERY ASSOCIATED WITH A PAPILLARY TRANSITIONAL CELL CARCINOMA

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Aneurysm of the renal artery is a rare pathological and clinical entity. The frequency of renal artery aneurysm at autopsy has been estimated as 1 in 11 000.[1] In 1951 Abeshouse in a review of the literature reported that 115 cases, including two of his, had been recorded.[2] Since then more have been reported, yet the total number still is under 150 reported cases. Poutasse has made the largest contribution to this series recording some twelve cases, which would lead one to suspect that perhaps renal artery aneurysms are more common than reports to date have indicated.[3]

An aneurysm is a localized abnormal dilatation of an artery due to disease of the media. A true aneurysm is one in which one or more layers of the vascular wall are distended. False aneurysms are formed by openings in the vascular wall with hematoma formation which later undergoes organization.[4]

The primary factor in the development of every aneurysm is a weakening of the arterial wall which is initiated by either a degenerative, inflammatory, congenital or traumatic lesion. Although the initial lesion may originate in either the wall, the lumen or outside the lumen of the renal artery, involvement of the medial coat is the prime prerequisite of formation of an aneurysm.

The symptom complex from aneurysm of the renal artery is rather varied, the most constant symptom is pain which is generally localized in the upper part of the abdomen and usually referred to the lumbar region of the involved side. Hematuria, palpable mass, hypertension, a bruit or pulsation may also be present.[4, 5]

Renal artery aneurysms generally occur in either the fifth to sixth decade and are equally represented in both sexes.[6]

The diagnosis of aneurysm is greatly facilitated by taking an x-ray, it is our most important diagnostic aid. The characteristic wreath or signet ring calcification medial to the renal pelvis is said to be pathognomonic. This appears to be true with saccular aneurysms but the majority of lesions are without calcification and aortography is the only means of demonstrating these types of aneurysms.[3, 5]

In a review of the literature many types of renal diseases were associated with aneurysms. Two cases of hypernephroma are reported,[3, 7] but I was un-

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ANEURYSM OF THE RENAL ARTERY ASSOCIATED WITH A PAPILLARY TRANSITIONAL CELL CARCINOMA

A. W. GEORDAN

Aneurysm of the renal artery is a rare pathological and clinical entity. The frequency of renal artery aneurysm at autopsy has been estimated as 1 in 11,000.[1] In 1951 Abeshouse in a review of the literature reported that 115 cases, including two of his, had been recorded.[2] Since then more have been reported, yet the total number still is under 150 reported cases. Poutasse has made the largest contribution to this series, recording some twelve cases, which would lead one to suspect that perhaps renal artery aneurysms are more common than reports to date have indicated.[3]

An aneurysm is a localized abnormal dilatation of an artery due to disease of the media. A true aneurysm is one in which one or more layers of the vascular wall are distended. False aneurysms are formed by openings in the vascular wall with hematoma formation which later undergoes organization.[4]

The primary factor in the development of every aneurysm is a weakening of the arterial wall which is initiated by either a degenerative, inflammatory, congenital or traumatic lesion. Although the initial lesion may originate in either the wall, the lumen or outside the lumen of the renal artery, involvement of the medial coat is the prime prerequisite of formation of an aneurysm.

The symptom complex from aneurysm of the renal artery is rather varied; the most constant symptom is pain which is generally localized in the upper part of the abdomen and usually referred to the lumbar region of the involved side. Hematuria, palpable mass, hypertension, a bruit or pulsation may also be present.[5, 6]

Renal artery aneurysms generally occur in either the fifth to sixth decade and are equally represented in both sexes.[6]

The diagnosis of aneurysm is greatly facilitated by taking an x-ray; it is our most important diagnostic aid. The characteristic wreath or signet ring calcification medial to the renal pelvis is said to be pathognomonic. This appears to be true with saccular aneurysms, but the majority of lesions are without calcification and aortography is the only means of demonstrating these types of aneurysms.[1, 5]

In a review of the literature many types of renal diseases were associated with aneurysms. Two cases of hypernephroma are reported,[3, 7] but I was un-

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Read at annual meeting of North Central Section of American Urological Association, Inc., Mackinac Island, Mich., August 28-31, 1957.

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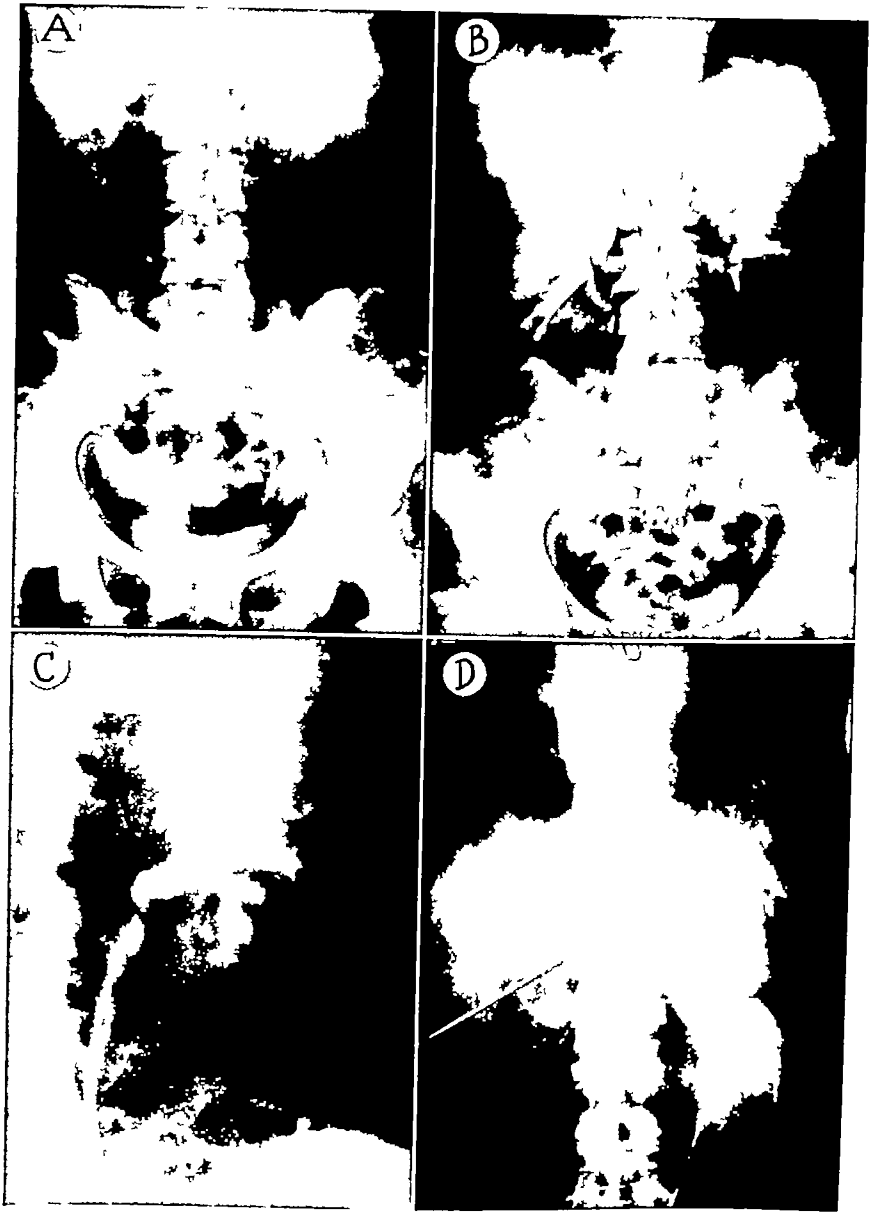

Fig 1

able to find one associated with a papillary transitional cell carcinoma This fact has prompted my report

Mrs J I, a 64-year-old white woman, was admitted to the Youngstown Hospital on December 7, 1956 with a six-month history of vague upper abdominal pain The pain was dull, constant, and at times would radiate to her left flank Her only complaint was a 12-pound weight loss during the preceding six

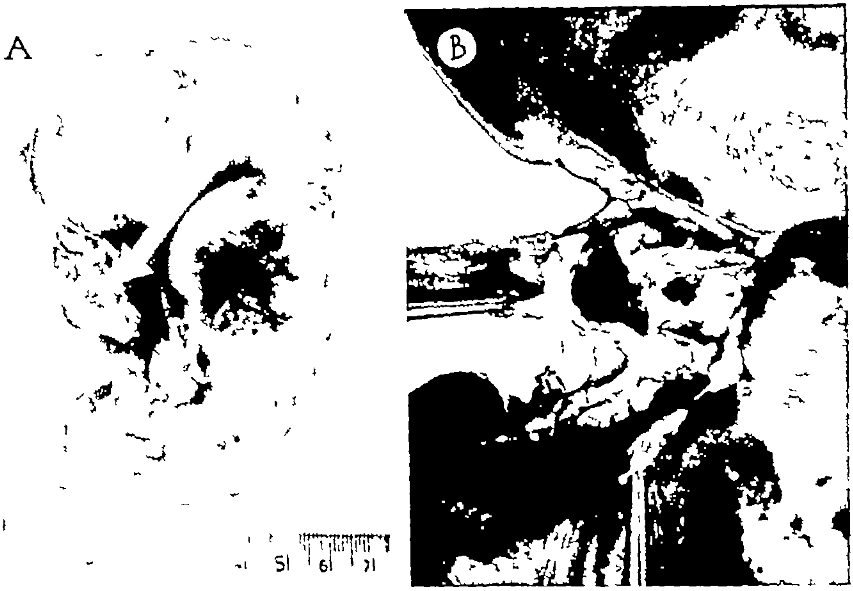

Fig 2

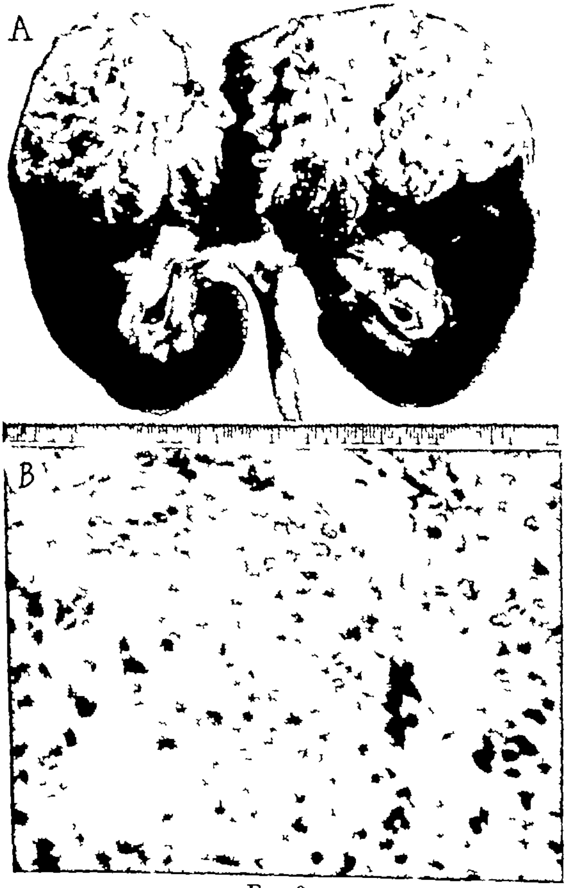

Fig 3

months which she attributed to a poor appetite She denied any gross hematuria or other urological complaints

Physical examination revealed a thin, well nourished white woman The blood pressure was 130/80, there was a pronounced pulsation of the mid-abdominal aorta, and a suggestion of a mass in the left upper quadrant Her laboratory work was not remarkable

A flat film of the abdomen (fig 1, *A*) showed a calcified wreath-like shadow situated medial to the left kidney Intravenous urography (fig 1, *B*) revealed a normal right kidney, on the left the calcific ring encroached on the renal pelvis, the superior calyx failed to fill and there was compression of the middle calyx A retrograde pyelogram (fig 1, *C*) showed essentially the same picture and we were unable to fill the superior calyx Aortography (fig 1, *D*) disclosed puddling of dye in the calcified ring A diagnosis of aneurysm of the left renal artery and possible tumor of the kidney was made

On December 26, 1956, under general endotracheal anesthesia, a transabdominal approach was performed which confirmed our diagnosis Following dissection and ligation of the aneurysm, the nephrectomy proceeded in the usual manner The patient made an uneventful recovery and was discharged on the fourteenth postoperative day

The pathological diagnosis (fig 2, *A*) was a large saccular aneurysm of the renal artery at the region of the bifurcation Figure 2, *B* shows a close-up of the renal artery, the aneurysm cut open, and the bifurcation of the renal artery In the upper pole of the kidney an irregular, oval, fairly well demarcated tumor was found (fig 3, *A*) Microscopically (fig 3, *B*) the tumor mass proved to be a papillary transitional cell carcinoma

SUMMARY

A case of aneurysm of the renal artery associated with papillary transitional cell carcinoma has been presented

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RENAL ANGIOMYOLIPOMA AND TUBEROUS SCLEROSIS

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The purpose of this paper is to present and discuss three patients in whom large benign renal tumors were present In two of these patients these tumors were present in both kidneys, while in the third only unilateral renal involvement is known All of these tumors were of the same composition, being hamartomas of the kidney or more specifically, angiomyolipomas

In the literature these tumors are sometimes described as being small with a greatest diameter of 1 to 3 cm observed only as incidental findings at autopsy[1] or again,[2-5] as large palpable masses, as is true in the cases we are presenting Approximately 50 per cent of these renal tumors occur in patients suffering with various stigmata of tuberous sclerosis[6] Manifestations of tuberous sclerosis do occur in two of the patients we will describe

Tuberous sclerosis was first described by Bourneville[7] in 1880 Clinically since that time this term has been used to describe patients with the triad of mental retardation, epilepsy and sebaceous adenomas of the face Tuberous sclerosis gets its name from the curious autopsy findings in the brain of individuals so afflicted Potato-like sclerotic patches are scattered indiscriminately over the surface of the cerebral cortex and are largely composed of neuroglial proliferations Fowler and Dickson[5] in 1910 described it as "congenital dislocation tumors" of the brain and that similar "dislocation tumors" not infrequently occur also in the skin, kidneys and heart of these same individuals They mentioned more rarely the appearance of similar tumors in the pancreas, duodenum, thyroid and breast Moolten[9] has stated that these hamartial tumors are characterized by numerous defects in tissue combination He has coined the term, tuberous sclerosis complex to denote homologous changes in organs other than the brain

No further attempt will be made in this paper to describe the cerebral pathology or theories as to the cause of this disease This has already been done by

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Read at annual meeting of North Central Section of American Urological Association, Mackinac Island Mich August 29–31 1957

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Bourneville D M Contributions a l'étude de l'idiote Sclérose tubéreuse des circonvolutions cérebrales idiotie et épilepsie hémiplégique Arch de Neurol , 1 81, 1880

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Moolten,[9] Inglis[10] and Critchley and Earl [11] Certainly it is generally agreed that these lesions originate primarily from ectoderm and mesoderm and that there is a strong hereditary factor

The majority of patients with recognized tuberous sclerosis described in the literature have been inmates of feeble-minded or mental institutions because of mental retardation These people, according to English[12] usually die in the first or second decade of intercurrent infection, status epilepticus, intracranial or visceral tumors or sudden heart failure Aside from this group of patients there is undoubtedly an even larger group who have tuberous sclerosis in a more mild form who go undiagnosed Accordingly, in 1942 Moolten[9] stated that the clinical diagnosis of the tuberous sclerosis complex is possible if two or more of the following features can be demonstrated mental retardation, epilepsy, adenoma sebaceum, phacoma, multiple mixed tumors of the kidney and a familial history of the disease

In addition to the lesion in the brain, adenoma sebaceum seems to be the most frequently associated finding These typically are small greasy nodules scattered in a butterfly pattern over the bridge of the nose and nasolabial folds Other skin lesions such as cafe au lait spots and periungual or subungual fibromata may be present Next in frequency and in well over 50 per cent of reported cases, are the tumors of the kidney These are usually hamartomas but sarcomatous changes have been described[13, 14] as have polycystic kidney disease However, as Allen[15] has pointed out, there are no recorded cases of metastases and the cases diagnosed as polycystic kidney disease may have been made erroneously on pyelographic evidence alone Benign tumors of the retina and optic nerve called phacoma[16] are also pathognomonic These are usually bilateral and easily recognized on inspection of the eye grounds as small glistening or chalky nodules arranged in clusters Roentgenographic evidence of the disease includes demonstration of calcifications in the brain, patchy zones of increased density in the skull[17] and discrete areas of dense bone in the vertebrae and ilium [18, 19] Holt and Dickerson[20] in a study of 43 patients with recognized tuberous sclerosis found in 66 per cent the same significant changes in the bones of the hands and feet

[10] Inglis, K Relation of renal lesions to cerebral lesions in tuberous sclerosis complex Am J Path , 30 739–757, 1954

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[18] Mertz, H O Tuberous sclerosis and renal tumor Trans Am Assoc Genito Urin Surg , 35 73–85, 1942

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These, they described as 'cyst-like foci in the phalanges and a rather distinctive type of periosteal new bone formation along the shafts of the metatarsals and metacarpals.'

With the foregoing information as background and review, we shall now proceed to the description of our cases.

CASE REPORTS

Case 1. V. L. C. (University Hospital No. 581086). A 40-year-old white married woman was admitted on January 29, 1956. One week previously she had consulted her family doctor because of vomiting and diarrhea. A diagnosis of gastroenteritis was entertained and because of the findings of an abdominal mass, x-ray films were made including an intravenous pyelogram. With a tentative diagnosis of polycystic kidney disease she was hospitalized for further evaluation. On admission she was free of symptoms. The past history was remarkable only in that an appendectomy and panhysterectomy had been done for "uterine fibroids and ovarian cysts" in 1954 in another hospital. The patient had never been pregnant and the family history was negative.

The patient was a healthy appearing woman of average normal mentality. The blood pressure was normal. The pertinent positive physical findings were as follows: White to tan tiny raised nodules on the nose and nasolabial folds (fig. 1), markedly thickened nails on all four extremities (fig. 2) with fibrous nodules under and adjacent to the toenails, hypertrophied, hyperkeratotic skin covering the palms of the hands and soles of the feet and two large palpable abdominal masses. The left abdominal mass extended from the costal margin down to three finger breadths above the pubic symphysis. The right abdominal mass was smaller and extended down to three finger breadths below the umbilicus.

Laboratory data: Normal urinalysis. Normal hemogram. Blood urea nitrogen 15 mg., 2-hour phenolsulfonphthalein test, 35 per cent. Blood serology negative. Routine urine culture, no growth. No abnormalities were seen on cystoscopy and retrograde pyelograms (fig. 3) were interpreted as showing changes characteristic

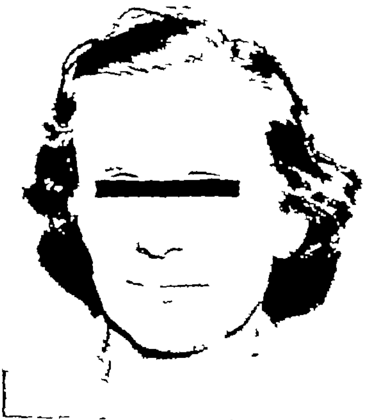

FIG. 1. Case 1. Adenoma sebaceum on nose and nasolabial folds.

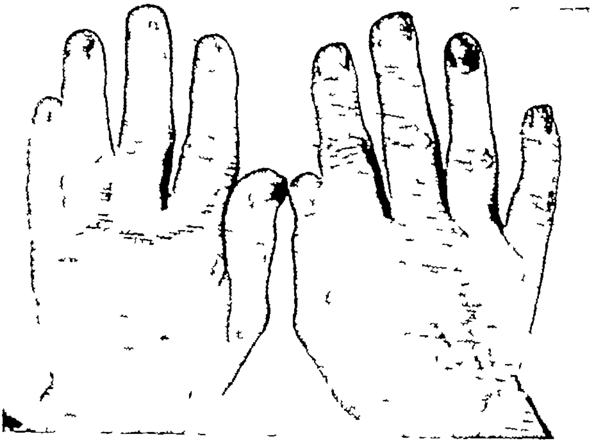

FIG 2 Case 1 Note dark hyperkeratotic fingernails

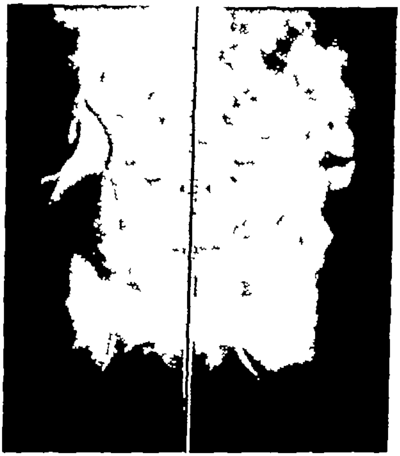

FIG 3 Case 1 Retrograde pyelograms show changes typical of polycystic kidney disease Increased calcific density of lumbar and thoracic vertebrae can be seen

of polycystic kidney disease It was also noted that there was increased calcific density of the lumbar and thoracic vertebrae

Consultation with a dermatologist was advised We then learned that she was currently under the care of a dermatologist, Dr Eldred Heisel His diagnosis was tuberous sclerosis because of adenoma sebaceum and periungual and subungual fibromas about the toenails He also felt that in her case the hypertrophic lesions on the palms of the hands and soles of the feet and the hyperkeratotic fingernails were due to tuberous sclerosis

An opthalmologic consultant described (fig 4) "two small raised white tumors on the retina of the right eye, one on the disk and one slightly medial thereto with a similar tumor near the disk of the left eye " His diagnosis was phacomata typical of tuberous sclerosis

More detailed x-ray films showed changes suggestive of osteoblastic thickening of the lamina, pedicles and bodies of the lumbar and dorsal vertebrae, patchy areas of increased density in the calvarium of the skull and several abnormal calcifications in the brain X-ray films of the hands (fig 5) and feet demonstrated cystic foci in the phalanges and irregular periosteal bone formation largely in the metatarsals

Abdominal exploration was negative except for the findings in both kidneys The renal masses were as large as described and both were studded with grayish blue and pink nodules ranging from 0 5 to 2 cm in diameter Perinephric fat was scanty and no normal appearing renal tissue was seen Both masses were biopsied and microscopic sections (fig 6) showed a tumor composed of smooth muscle, numerous small capillaries and fat tissues Diagnosis angiomyolipoma of both kidneys

The postoperative course was not remarkable and the patient has been in good health since then

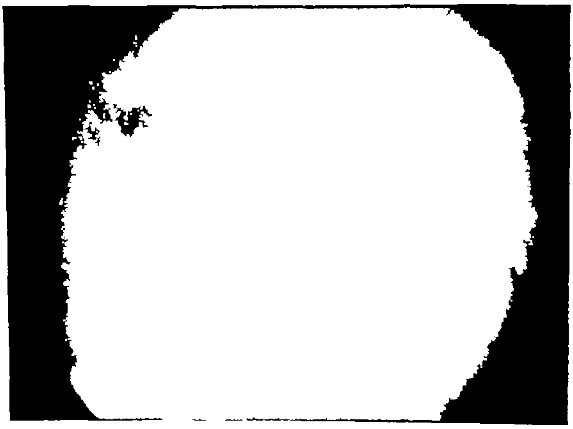

Fig 4 Case 1 Right retina shows two phacomata near optic disk

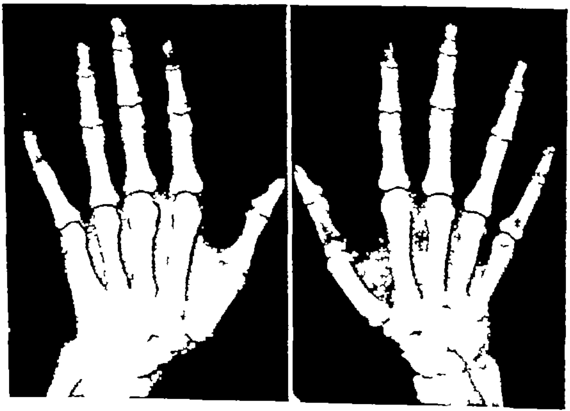

Fig 5 Case 1 X-ray films of hands show scattered cystic areas in phalanges and irregular cortical thickening of proximal phalanges and metacarpals

The next case was discovered through our pathologist who stated that after nephrectomy on our own general surgery service a similar large renal tumor had been found two years previously

Case 2 O M G (University Hospital No 543566) A 42-year-old white woman was admitted on April 28, 1954, because of a two-year history of intermittent dull ache in the left midabdomen The past history was remarkable in that she had a right radical mastectomy elsewhere for "cancer of the nipple" 10 years previously and had given birth to 8 children

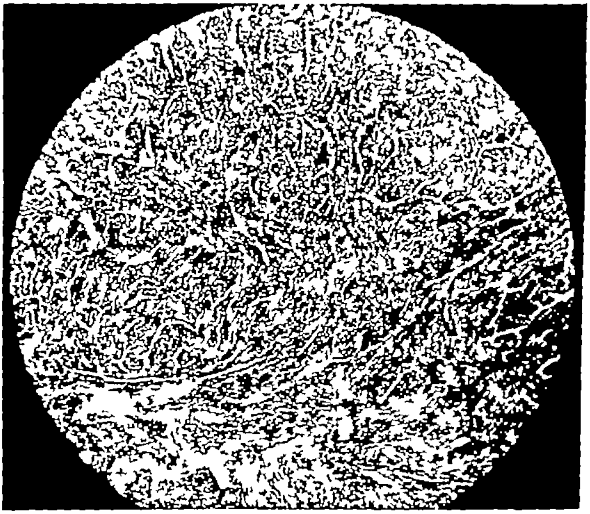

Fig 6 Case 1 Photomicrograph of tumor from right kidney shows smooth muscle with hyalinization and numerous capillaries Other sections of biopsies from kidney showed areas of fat tissue

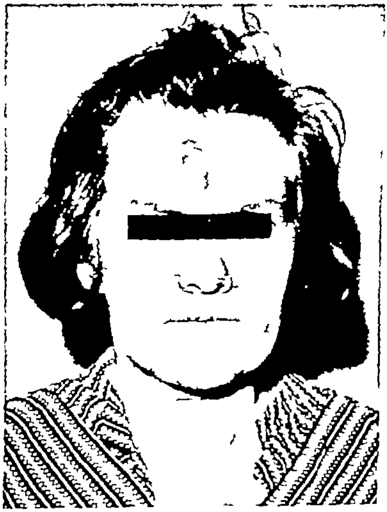

Fig 7 Case 2 Adenoma sebaceum of nose and nasolabial folds may be seen Nature of dark raised lesion on forehead is unknown

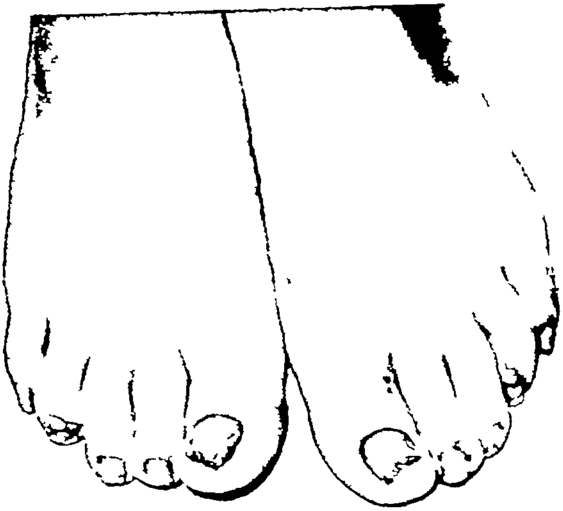

FIG 8 Case 2 Note subungual fibroma of left great toe and periungual fibromas, best seen on both fourth toes and left second toe Similar fibromas present in case 1

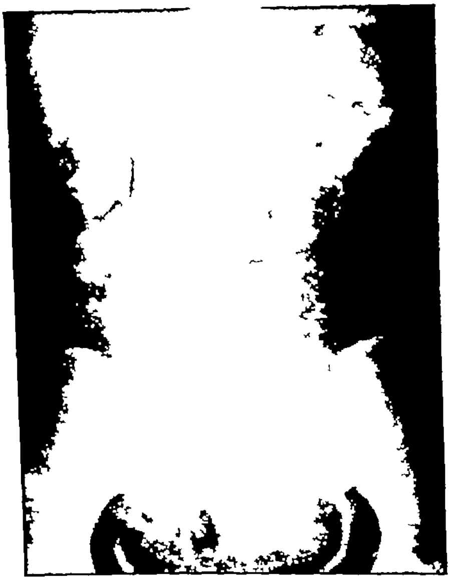

FIG 9 Case 2 Retrograde pyelogram shows distortion of inferior calyces bilaterally, suggestive of parenchymal tumors or cysts

On physical examination the blood pressure was 134/88 Pertinent positive physical findings were as follows an elevated dark brown lesion of the skin of mid forehead measuring 4 by 2 cm , scattered tiny tan nodules on both sides of the bridge of the nose and nasolabial folds (fig 7), thickened nails on all four extremities with periungual and subungual firm masses, limited to the toes (fig 8) Surgical absence of the right breast and a large firm, palpable, slightly movable mass in the left upper quadrant extending from the umbilicus up and beyond the rib margin anteriorly were noted

Laboratory data Normal hemogram and urine analysis Blood urea nitrogen was 18 mg Blood serology negative A 2-hour phenolsulfonphthalein test, 70 per cent X-ray films of the chest and entire gastrointestinal tract were interpreted as being normal Retrograde pyelograms were interpreted as possible bilateral renal tumors or polycystic kidney disease (fig 9) Renal arteriograms were unsatisfactory for diagnosis

On August 16, 1954, because of a preoperative diagnosis of left retroperitoneal tumor, through an abdominal incision, left nephrectomy was performed The entire mass weighed 1375 gm (fig 10) The kidney proper was studded with yellow nodular tumors of varying size with a large, encapsulated, roughly ovoid mass at the lower pole measuring 21 by 13 by 8 cm There was no perinephric fat Frozen sections suggested hamartoma, and right renal exploration was advised Inspection of the right kidney showed a smaller renal mass but tumor involvement similar to that noted in the left kidney Biopsy was not done Grossly, on section the left kidney was studded with yellow nodules like adipose tissue which seemed almost entirely to replace the renal parenchyma There was no cleavage plane between the kidney and tumor mass

Pathologist's report "Multiple sections of the kidney and attached mass show the kidney to be invaded by several types of tissue consisting mainly of adipose tissue, numerous thick walled blood vessels and cells concentrically around former which with trichrome stains are benign variations of smooth muscle Diagnosis Angiomyolipoma "

Postoperative course was uneventful and the diagnosis of tuberous sclerosis was *not* made

Several months ago we had the opportunity to re-examine this woman and

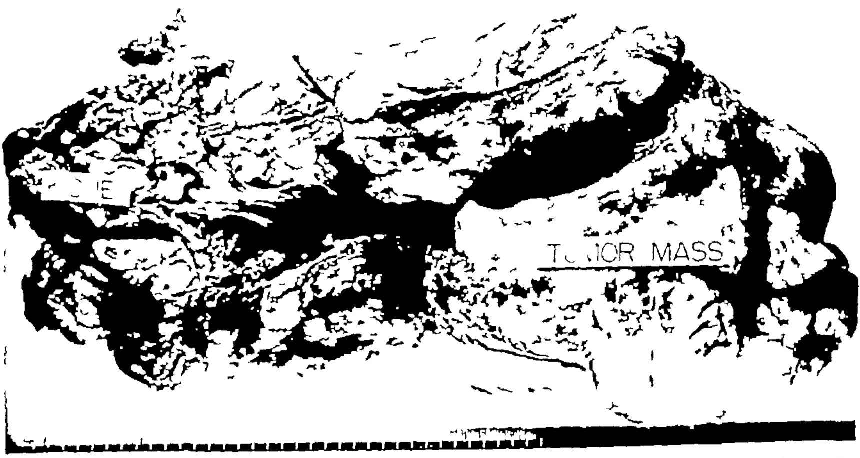

FIG 10 Case 2 Surgical specimen Cut surface of kidney shows many nodules which resemble fat scattered throughout renal parenchyma

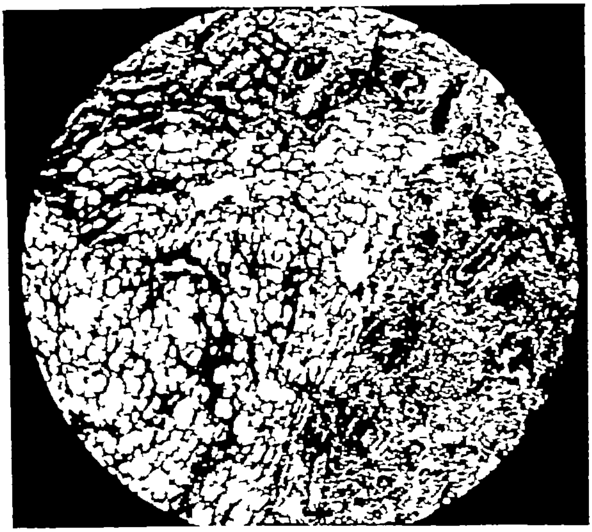

Fig 11 Case 2 Photomicrograph of tumor shows fat cells, blood vessels and masses of perivascular smooth muscle Normal renal tubules are present at 12 o'clock

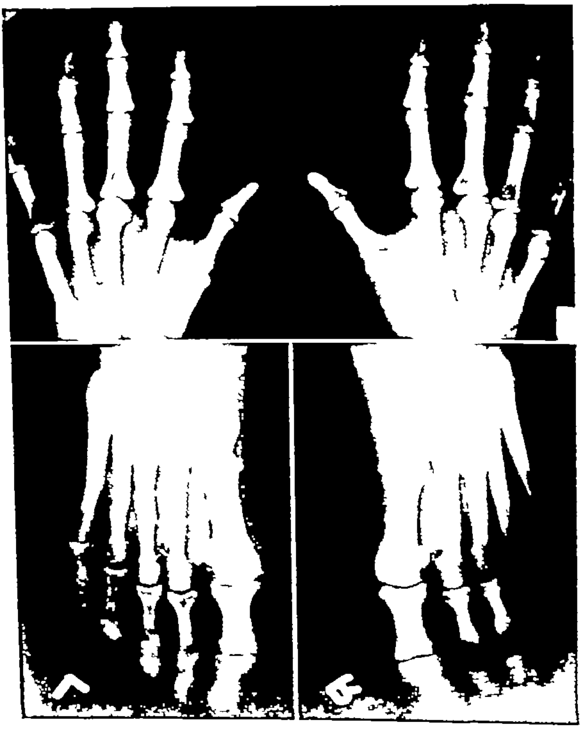

Fig 12 Case 2 X-ray films of hands and feet show cystic foci in phalanges and periosteal new bone formation along shafts of metatarsals

found her to be in good health and of low average mentality The family history was pertinent in that four of her 8 children were definitely mentally retarded and that a fifth child had recently been an inmate of one of the state's feebleminded institutions They described this child as showing the classic picture of tuberous sclerosis with epilepsy, mental retardation, adenoma sebaceum and numerous cafe au lait spots on the trunk and extremities

Another intravenous pyelogram showed no essential change in the right pyelogram X-ray films of the skull showed areas of calcification in the calvarium within the brain substance X-ray films of the hands and feet showed random cysts in the phalanges and irregular thickening of the cortex of the metatarsals and metacarpals (fig 12) Examination of the eye grounds by an ophthalmologist failed to reveal any abnormalities

Case 3 L S (University Hospital No 581211) A 40-year-old white married woman was first admitted on January 31, 1956 Two months previously she had experienced a brief episode of severe left flank pain which recurred 10 days before admission There had been some associated fever but no urinary symptoms Past history left salpingo-oophorectomy, elsewhere, for "tumor" in 1948 Complete hysterectomy, elsewhere, for "uterine tumors" in 1953 Family history noncontributory Two healthy teen-age children No unusual physical findings

Laboratory data Normal hemogram except for mild anemia Normal urinalysis Two-hour phenolsulfonphthalein test, 60 per cent Blood serology normal X-ray film of chest normal Cystoscopy negative except for two ureteral orifices

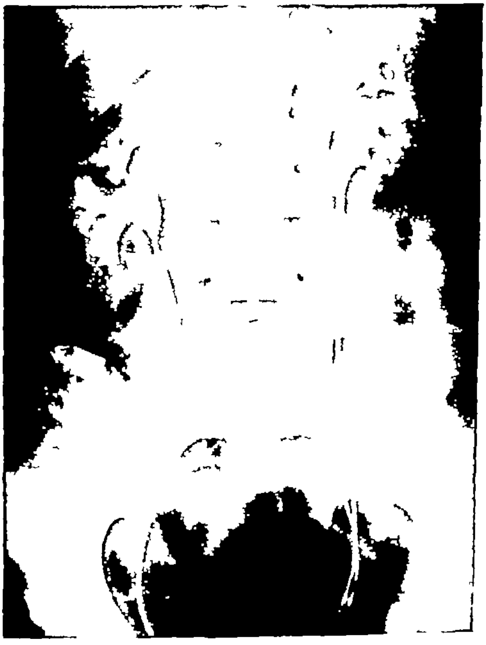

FIG 13 Case 3 Retrograde pyelograms show irregular filling of left lower pole calyces with "droopy" appearance Left renal outline not seen

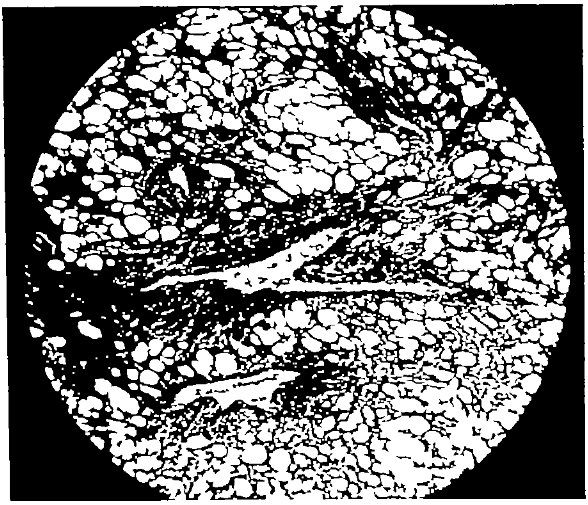

FIG 14 Case 3 Photomicrograph of tumor shows angiomyolipoma, i e , fat cells, blood vessels and masses of perivascular smooth muscle

on the left Retrograde pyelograms showed a normal right upper urinary tract, complete reduplication of left ureter and pelvis with the left lower pyelogram showing a distorted, droopy appearance (fig 13)

No positive diagnosis was made and the patient was discharged home to await the results of urine studies for tuberculosis The patient was re-admitted on March 29 because of severe left flank pain with associated vomiting She appeared acutely ill and had marked tenderness in the left costovertebral angle Laboratory data were essentially the same as on previous admission

On March 30 a left nephrectomy was performed through a lumbar flank incision Grossly it appeared that a large necrotic renal tumor was present which had ruptured, with associated hemorrhage Microscopic sections (fig 14) and pathologist's report Hemorrhagic infarct of kidney and tumor Tumor composed of angiomyolipoma

The postoperative course was uneventful The right kidney was not explored A thorough survey showed no evidence of stigmata of tuberous sclerosis The patient has been well since that time

DISCUSSION

Tuberous sclerosis as such, and clinically significant hamartomas of the kidneys as such, are fairly rare entities However if one of these diagnoses is proven it is highly probable the other entity is also present Our own experience, as illustrated in the first two cases presented, suggests how easily the diagnosis of tuberous sclerosis can be missed These same two cases also suggest that hamartial renal tumors should be considered in the differential diagnosis of polycystic kidney disease

Case 3, we believe, is an example of unilateral renal angiomyolipoma in a patient who does not have tuberous sclerosis This patient came to nephrectomy solely because of symptoms secondary to hemorrhage and necrosis of the tumor It is worthy of note that this was precisely the course of events and the operative findings in cases previously reported by Morgan and his co-authors,[4] Heckel and Penick[3] and Rusche [2]

Even though all three of our patients were women in their early forties, a study of the literature indicates a probable equal occurrence of these diseases in males

SUMMARY

Manifestations of tuberous sclerosis complex are discussed with emphasis on the frequently associated renal hamartomas

Three cases are presented in which renal angiomylopomata of clinical sig-significance occurred In two of these patients multiple manifestations of the tuberous sclerosis complex are demonstrated

We are indebted to Drs Edwin H Ellison, William H Havener, Eldred B Heisel and Hans G Schlumberger for their contributions to these case studies

ADDENDUM

Case I experienced a large left perinephric hemorrhage in October 1957 Hemoglobin dropped to 8 8 grams per cent In view of the diagnosis, she was treated conservatively with transfusions and recovered She has been well since that time

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EPITHELIAL TUMORS OF THE RENAL PELVIS AND URETER

LLOYD B. GREENE, BENJAMIN L. HAYLLAR AND MORTON BOGASH

From the Urologic Service of the Pennsylvania Hospital, Philadelphia, Pa.

Primary epithelial tumors of the renal pelvis and ureter were formerly thought to be rare. However in the last two decades several authors have written of their not uncommon occurrence.[1, 2] The greater number of these tumors noted recently is probably due to both more accurate diagnosis and a real increase in the incidence.[3] These tumors represent almost 14 per cent of all primary renal tumors and slightly more than 80 per cent of primary ureteral tumors.[2, 4] The vast majority of such tumors are malignant.

The commonly accepted treatment for epithelial tumors of the upper urinary tract is nephro-ureterectomy with removal of a cuff of bladder surrounding the intramural ureter when not contraindicated by the status of the other kidney and the patient's general condition. The papilloma of the upper urinary tract, although classified as a benign tumor, should be treated similarly because of its tendency to multiplicity and recurrence.

The records of 33 patients who had primary epithelial tumors of the renal pelvis and/or ureter were reviewed. The patients were treated by the senior author (L.B.G.) and his associate (B.L.H.) during the period from 1942 to 1957. Some pertinent data have been summarized in table 1.

Of the 26 patients with transitional cell tumors, 22 had tumors of the renal pelvis. Seven of these patients also had ureteral and/or bladder tumors. Ten ureteral tumors were noted, 8 of which were associated with pelvis and/or bladder tumors. Of the initial upper tract tumors, 17 were papillary carcinomas, six flat carcinomas and three papillomas.

Five patients had recurrences or new tumors. Three had recurrences in the ureteral stump and four in the bladder. Four of the five had multiple recurrences. Recurrent bladder tumors subsequently developed in one patient treated by nephro-ureterectomy. Four patients treated by more conservative methods acquired ureteral and/or bladder recurrences. In four of 26 patients it was believed that tumor was left at the time of the operation. None of these four patients survived.

Of the 26 patients, two are omitted when calculating survival because of inadequate data. Table 2 demonstrates the distribution of the group in terms of length of survival. Eight deaths were due to the neoplasm and two deaths to unknown causes.

Accepted for publication June 13, 1957.

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TABLE 1

	Transitional	Squamous
Number of patients	26	7
Age (average—yrs)	64 7	60 9
Male Female	2 1	1 3 1
Hematuria	24	2
Calculi	1	6
Symptoms until diagnosis (average mos)	24	?
Obstruction	13	6
Diagnosis by intravenous pyelogram	13	?
Diagnosis by retrograde pyelogram	23	?
Infection	11	7
Treatment		
Nephrectomy	14	6
Nephro ureterectomy		
Simultaneous	4	1
Later	5	0
Partial ureterectomy	1	0
Others	2	0

TABLE 2 *Survival following treatment for transitional cell tumors*

Years	0-½	½-1	1-2	2-3	3-4	8-10
Living (14)	1	4	4	1	3	1
Dead (10)	5	0	3	0	1	1

DISCUSSION

The patient material corresponds well to that described previously in the literature Males predominated over females in the ratio of 2–1 with the average age of incidence being in the sixth decade for both the squamous cell tumors and the transitional cell tumors[1, 2, 5]

The squamous cell tumors had the expected poor clinical course with no five-year survivals and the usual death within one to two years after operation[5] Infection and obstruction were present in nearly all and calculi were present in over one-half

The transitional cell tumors encountered in this group of patients showed the expected distribution of tumor type with the largest group of patients (70 per cent) having papillary carcinomas The known tendency towards multiplicity and recurrence of tumors was noted in that nine of 26 patients had multiple tumors and five had recurrences Three people had recurrences in the ureteral stump and the remainder in the bladder Multiple or recurrent upper urinary tract tumors were all unilateral In two-thirds of the cases bladder involvement when present was on the same side as the upper tract lesion These observations seem to favor implantation rather than a carcinogen as the major cause of multiplicity and/or recurrence

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TABLE 3 *Factors influencing survival in transitional cell tumors*

	Tumor Grade			Ureteral *Location*	Extension 3+ to 4+	Multiplicity and/or Recurrence
	0–1	2	3–4			
Living (14)	5	7	2	4	3	3
Dead (9)	0	4	5	5	5	5

23 of 26 patients' records and pathologic material permitted this type of evaluation

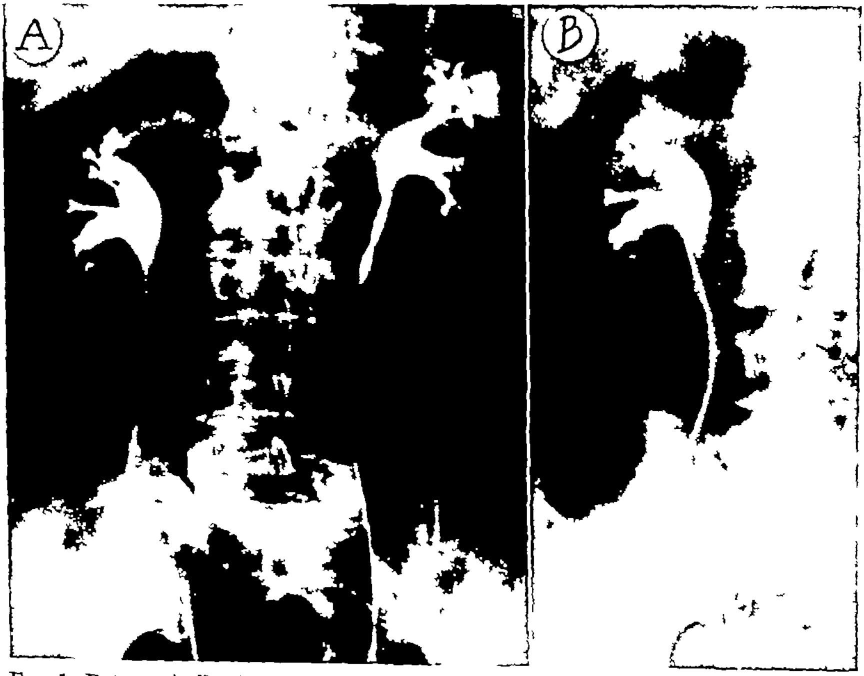

FIG 1 Patient A D *A*, retrograde pyelogram, made during first episode of hematuria from right side, interpreted as negative *B*, retrograde pyelogram made during second episode of hematuria from right side that occurred eight months after first Note large space taking lesion in calyx of right upper pole Diagnosis Papillary carcinoma of calyx of upper pole

In this series multiplicity of tumors, high grade of microscopic malignancy by Broders' classification, location of one of the tumors in the ureter, and deep extension of the tumor into tissues of the urinary tract and/or into adjacent tissues appear to be bad prognostic signs with a higher incidence of these findings demonstrable in the group of non-surviving than in the living (table 3) [1, 6, 7]

The delay in diagnosis of transitional cell tumors was almost two years This was despite the fact that hematuria was the initial sign in all but two patients Unfortunately four patients had suspicious x-rays for a period of two years before the final diagnosis was made However, because of poor patient co-opera-

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tion adequate followup was not possible Of these four patients, three are dead The necessity for thorough followup is demonstrated by x-rays (fig 1) of one patient (A D) Hematuria occurred from the right side eight months before the diagnosis was made An original ureteropyelogram at the time of hematuria was negative A right ureteropyelogram approximately eight months later showed a large papillary lesion of the upper pole calyx Adequate radiologic visualization of the entire ureter is essential for accurate diagnosis It is hoped that cytologic methods of study will be helpful in investigating patients in whom tumor of the upper urinary tract is suspected

The followup period is not sufficiently long in many of these cases to say much about survival other than simply to list the data, as has been done in table 2 No correlation was seen between the type of treatment and the survival but it should be noted that three patients had recurrences in the ureteral stump and all of these patients died

SUMMARY

The records of 33 patients with primary epithelial tumors of the upper urinary tract were reviewed Seven had squamous cell tumors and 26, transitional cell tumors No patient with a squamous cell tumor survived five years Most of these patients died within one year following operation The patients with transitional cell tumors enjoyed longer survival High grade of malignancy by Broders' classification, extensive local disease, multiple tumor sites and location of a tumor in the ureter were unfavorable factors The best hope for cure lies in early diagnosis and prompt radical surgical therapy (nephroureterectomy) whenever such is permitted by the condition of the patient

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NONSPECIFIC URETERITIS ELUCIDATED BY A CASE OF PRIMARY URETERITIS

OVE NORING

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While ureteral calculi are among the common possibilities to be considered in the diagnosis of acute abdominal conditions, inflammatory lesions of the ureter are seldom encountered in a department of general surgery. Most surgeons are never confronted with ureteritis apart from the secondary variety which is caused by widespread pyonephrosis, predominantly by tuberculous pyonephrosis.

Israel and Israel have described two types of secondary, nonspecific ureteritis. One, caused by obstruction, manifests itself as a dilated, flaccid, thin-walled, gradually elongated and corkscrew-like tortuous ureter with a hyperemic, sometimes ulcerated mucosa. The other, nonobstructive variety is due to propagation from pyonephrosis. In this type, the ureter is stiff, narrow, straight, and shortened, surrounded by a thick periureteral sheath which often adheres to the surrounding structures. The muscular coat exhibits a more or less fibrous degeneration, and gradually circular strictures develop, perhaps even extensive obliteration which may transform the ureter into a fibrous cord.

As for more special varieties (Kaufmann, Henke and Lubarsch), it is worth mentioning ureteritis polyposa with the widespread polypous hypertrophy of the ureteral mucosa, ureteritis membranacea, in which large flakes of fibrin may be present in the urine due to pronounced fibrinous exudation from the ureteral mucosa (Israel and Israel), and ureteritis cystica which often co-exists with the not infrequent cystitis cystica whose typical cystoscopic appearance is illustrated in several textbooks.

These last-mentioned varieties are of obscure etiology, but there is also secondary ureteritis and periureteritis representing encroachment of the inflammation from surrounding tissues. Such adhesive or plastic periureteritis has been reported in part as a sequela of periappendicular abscess (Trabucco and Marquez), in part as a possible sequela of previous prostatic and urinary lesions (Vest and Barelare), and in part due to chronic inflammation of the periureteral connective tissue leading to hydronephrosis (Chisholm and associates, Ormond, Amselem, Miller and associates). Spastic ureteritis is also said to occur in the presence of diseases affecting the female genitalia, prostate, seminal vesicles, or diverticulitis of the colon (Thackston, Price and Richardson).

Primary nonspecific (idiopathic) ureteritis must be extremely rare, as it does not seem to have been reported by others than James Israel who published his case as early as 1893. His patient was a 28-year-old man who had been suffering from pollakiuria, dysuria, severe and frequent renal colic on the left side, and frequent hematuria for 8 years. His history was negative for tuberculosis and gonorrhea. Cystoscopy failed to show abnormal conditions. Exploratory opera-

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tion revealed that the left kidney was normal with only a slight dilatation of the pelvis and calyces As the symptoms persisted, operation was repeated, but no abnormality was demonstrable upon intrapelvic palpation The ureter was thickened to three times its normal width, in several places it was as hard as cartilage and adhered to the posterior abdominal wall However, a bougie size 10 was passed the entire length of the ureter Pyelostomy was performed, but as the symptoms were not relieved, nephro-ureterectomy had to be done at a later date The ureteral thickening involved particularly the mucosa and the muscular coat which exhibited pronounced leukocytic infiltration The kidney was normal, the pelvis and calyces slightly dilated

CASE REPORT

A gas-worker, aged 41, had been previously treated here in 1950 and 1954 for anal fissure and for right inguinal hernia and hemorrhoids by dilatation of the anus, herniotomy, and extirpation of the hemorrhoids without complications He had no urinary complaints Routine studies were within normal limits

In October 1956 the patient was admitted because of his urinary complaint One month previously he had suffered moderate, constant, nonradiating pain in the region of the left kidney He also had pollakiuria, cloudy urine, and elevated temperature, up to 39 4C and severe fatigue At home, he had been treated by bed rest and sulfa drugs with a fairly good effect, but when the pain, which did not at any time suggest renal colic, began to spread down to the symphysis and the fatigue persisted, he was sent to the hospital Before admission, he had not had hematuria, cardiac, pulmonary, or intestinal complaints, and he had never been exposed to gonorrheal or tuberculous infection

On admission, the patient was not debilitated, but in a good general condition and without pain His temperature was 37 8C, pulse rate 64, blood pressure 125/85 He was not anemic His tongue, fauces, and auscultation of heart and lungs were normal On palpation of the left kidney, he complained of slight tenderness, especially upon percussion The scar after the right herniotomy was sufficient The genitalia were normal, in particular there was no epididymitis or signs of enlargment or tenderness of the prostate or seminal vesicles

During the subsequent days, the temperature was normal Erythrocyte sedimentation rate was 43, hemoglobin 95 per cent, blood urea 34 mg per cent The urine did not contain protein, erythrocytes, or casts, but numerous leukocytes Culture revealed gram-negative rods resistant to penicillin and sulfathiazole An electrocardiogram and x-rays of the heart and lungs failed to show any abnormality

X-rays of the urinary tract did not reveal any calculi After intravenous injection of a contrast medium, rapid excretion was seen in both kidneys On the left, the calyces were large and plump and the pelvis considerably dilated (fig 1, *A*) At this site, the contrast medium was held up for some time, suggesting an obstruction The upper portion of the ureter appeared to be slightly dilated, and on one film the ureter seemed to emerge from the lateral aspect of the pelvis Diagnosis Left hydronephrosis

Cystoscopy revealed a normal bladder mucosa without any signs of inflammation, ulceration, tumors or stones The ureteral orifices were normal A ureteral catheter could be passed 25 cm without meeting any obstruction Retrograde pyelography showed on the left, on a level with the fifth lumbar vertebra transition from a dilated caudal segment of the ureter to a constricted ureteral canal through which only a little contrast passed to the pelvis (fig 1, *B*) The findings indicated a space-occupying lesion compressing the ureter in an area 6–7 cm in length, immediately below the pelvis

On October 19 left nephro-ureterectomy through a lumbar incision was performed under thiopentone-cyclopropane-curare anesthesia with intubation First the ureter was isolated In the cranial 8–10 cm it was reduced to the thickness of a slate pencil, whereas the caudal segment was dilated, with a brittle, thickened wall adhering to the surroundings particularly to the psoas major In several sites, moreover fibrin-like coatings were seen on its adventitia The renal pelvis was about the size of a small orange and somewhat tense, the upper calyx seemed to be cut off from the remaining part of the pelvis, lying as a retort-shaped structure above the pelvis

The kidney and the entire left ureter were removed the ureter being cut close to the bladder and ligated with catgut Three drains were inserted 2 gm streptomycin and 2 million units penicillin poured into the operative cavity, and the wound closed in layers with catgut The postoperative course was uneventful

The operative specimen proved to contain in the pelvis purulent urine, but no stones There were no gross changes of the kidney The emergence of the ureter was normal, down from the pelvis In its caudal 15 cm it was dilated, showing inflammatory thickening of the wall The mucous membrane showed longitudinal folds with greyish brown coatings and ulcerations There were no

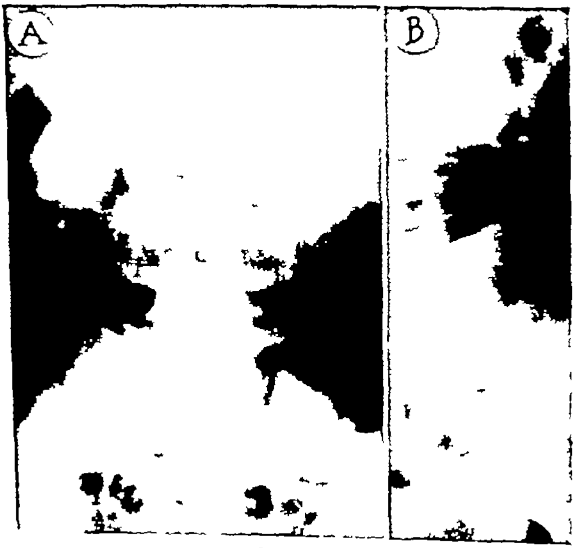

FIG 1

valves or strictures The cranial 10 cm of the ureter were slightly constricted, but at the narrowest site the circumference was 5 mm No inflammatory changes were seen in this ureteral segment

Microscopic examination of various sections of the kidney showed no abnormality anywhere, and no signs of acute or chronic inflammation, dilatation of the canal system, or vascular changes There was mild edema of the pelvic wall, but the epithelial lining was normal In the caudal, dilated part of the ureter, there were morbid changes characterized by widespread and pronounced leukocytic infiltration, in places with abscess formation (fig 2), and edema The mucosa was destroyed in many places and replaced by a thick, necrotic, and partially blood-tinged coating In some places, the small abscesses extended through the tunica muscularis into the periureteral connective tissue and fat, where fibrinous exudation and leukocytic infiltration were present There were no foreign bodies, tuberculous changes, or tumor formation The histological findings appeared to indicate that the inflammation originated from the inner layers of the ureter rather than having come from without However, it was impossible to elucidate the cause of this strange, severe inflammation, not even by using special stains

The patient was re-admitted for followup 6 months after the operation At that time, he had no symptoms apart from fatigue Urination was completely normal Temperature normal, blood pressure 125/75, erythrocyte sedimentation rate 8 mm /hr , hemoglobin 94 per cent, eosinophilic cells normal, Wassermann reaction and gonococcal complement fixation test negative, antistreptolysin titer normal Urine without protein or other abnormal components, no bacteria, also no tubercle bacilli on culture Cystoscopy showed that the bladder mucosa was still normal, without inflammatory changes The right ureteral orifice was normal The left one presented itself as a delicate, closed slit showing no reaction Intravenous pyelography revealed a normal right pyelogram with rapid excretion and free passage to the bladder

Case summary A 41-year-old man was admitted after one month's urinary

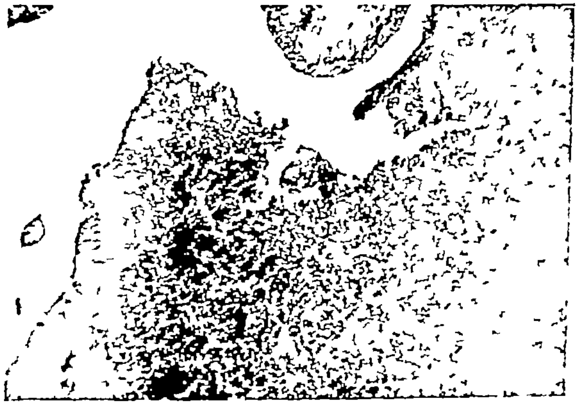

FIG 2

complaints, fever and constant left flank pain relieved by sulfonamide medication, pollakiuria, cloudy urine, and fatigue Investigations in the hospital revealed an elevated erythrocyte sedimentation rate and hydro-(pyo-)nephrosis Operation disclosed severe, acute ureteritis The renal pelvis and calyces were greatly dilated with purulent urine, but the kidney proper was normal After nephro-ureterectomy the patient made an uneventful recovery, and at follow up, six months later, he was still in good health

DISCUSSION

Since the available literature does not contain one case of primary ureteritis apart from that reported by Israel in 1893, one may of course doubt its existence It can probably not be ruled out entirely that this was a case of primary renal coliuria, although no morbid changes were demonstrable in the kidney at the time of operation It is beyond doubt, however, that the main site of the disease, at the time of operation, was in the caudal half of the ureter The histological findings were striking, indicating a highly acute nature of the lesion and showing a tendency to abscesses which would not appear to suggest a typical coli inflammation and which very seldom has its parallel, even in the most severe cases of cystitis Theoretically, it cannot be ruled out that a small stone has passed through the ureter, where it has given rise to small injuries leading to inflammation, but the absence of hematuria and of colicky pain militates against this possibility It is, thus, impossible to advance any definite explanation of the primary onset of the inflammation in the ureter The possibility of an underlying primary connective-tissue disorder has been considered, but the blood findings do not indicate such a disorder The cause of the hydro-pyo-nephrosis is not quite obvious, as no actual ureteral obstruction was demonstrable The same applied to Israel's patient The hydronephrosis must be assumed, therefore, to have been due to dynamic factors in the form of reduced contractility and elasticity due to the pronounced inflammatory infiltration in the caudal half of the ureter combined with a state of spastic contraction in its cranial half

On the basis of the one reported case, it is of course impossible to set up any lines for the treatment of primary ureteritis According to Israel and Israel, a ureter with inflammatory changes in its deep muscular layers will not regain its elasticity or contractility, but will remain the site of secondary, widespread strictures For this reason, they do not recommend pyelostomy or nephrostomy, as this would inevitably lead to a urinary fistula At the time of operation in the present case, we were in no doubt that any plastic intervention on the ureter would be useless On the other hand, it was of course not without hesitation that we performed nephrectomy in an inflammatory condition which had not given rise to definite gross changes of the kidney It is impossible to know whether antibiotic therapy could have cured the patient entirely without leaving secondary shrinkage and strictures, but this seems very unlikely Nevertheless, the author is inclined to agree with Vest and Barelare who published their four cases of periureteritis plastica with the wish that "others with similar cases may apply proper corrective surgery without sacrifice of renal structure "

SUMMARY

After briefly reviewing the varieties of nonspecific ureteric inflammation, the author reports the case of a 41-year-old man with moderate, constant flank pain, pollakiuria, cloudy urine, and fatigue On the basis of the operative and histological findings the case was diagnosed as primary ureteritis The treatment of this condition is discussed

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FURTHER OBSERVATIONS ON PHARMACOLOGIC REACTIONS OF THE BLADDER

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Medical literature abounds with reports of disturbances in urination produced by drugs of various types The drugs purported to influence the activity of the bladder or the urinary sphincters can be classified as adrenolytic,[1] adrenergic,[2, 3] anticholinergic,[2, 4, 5] cholinergic[2, 6, 7] and antihistaminic[2, 3, 8] Modern concepts of bladder physiology indicate that only the cholinergic and anticholinergic drugs should affect urination In view of the discrepancy it was decided to investigate the reaction of the bladder to typical drugs from each category This report is divided into two main sections The first part deals with the experimental investigation of the drugs while the second section describes the clinical use of some of the drugs altering bladder function

PART 1

Methods and materials In order to obtain objective information, paraplegics with reflex neurogenic bladders were employed as the initial subjects These patients have spinal cord lesions completely interrupting sensory and corticoregulatory tracts at a level higher than the sacral spinal cord Reflex bladders are characterized by lack of sensation and lack of cortical control resulting in uncontrolled or uninhibited contractions of the detrusor When the reflex neurogenic bladder is filled with urine or fluid, proprioceptive endings are stretched and sensory impulses are initiated, they travel along afferent fibers to the spinal cord where they impinge upon the motor neurones of the bladder and cause them to discharge The motor impulses then travel over parasympathetic fibers, ganglia and neuromuscular junction to stimulate contraction of the vesical musculature Within limits the investigator can stimulate bladder contractions

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Read at annual meeting of North Central Section of American Urological Association, Mackinac Island Mich, August 29–31, 1957

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TABLE 1

Compound	Type	Dosage	Route of Injection
Ephedrine	Adrenergic	0 075 gm	I V
Regitine	Adrenolytic	0 010 gm	I V
Urecholine	Cholinergic	0 007–0 0010 gm	Subcutaneous
Neostigmine	Cholinergic	0 004 gm	Subcutaneous
Banthine	Anticholinergic	0 050–0 100 gm	I V
Atropine	Anticholinergic	0 0012 gm	I V
Benadryl	Antihistaminic	0 050–0 075 gm	I V
Pyribenzamine	Antihistaminic	0 050–0 075 gm	I V

at will in these patients by filling the bladder with a certain volume of fluid at a set pressure and rate of flow, and these contractions can be reproduced during several runs provided an adequate rest period is allowed between fills The paraplegic is the most physiological subject for these studies because anesthesia is not needed, the bladder with its lower reflex arc is intact and varying cortical influences are eliminated

Cystometry[9] was used in evaluating the bladder reactions to the drugs The cystometric apparatus was connected to an inlying urethral catheter in some patients and to a suprapubic cystostomy tube in others At least two control cystometric examinations were performed in each patient prior to the administration of a drug Patients with marked variability in their control cystometrographs were eliminated as subjects All drugs were administered parenterally and in dosages usually higher than those recommended for routine use After an appropriate time interval, usually 10–20 minutes after injection, several cystometrographs were obtained again Some patients agreed to have all of the drugs given to them while others permitted the administration of only two or three drugs Each drug was tested in ten patients

Table 1 outlines the types of compounds utilized, their dosages and routes of administration

After completion of administration of the drugs to the patients with reflex neurogenic bladders, the various compounds with the exception of atropine were tested in subjects with normal bladders, some of these were medical students and house staff The subjects were advised to present themselves to the investigator when they had a strong desire to urinate At this time they were given an injection of one of the drugs and instructed to attempt to empty their bladders within 10–20 minutes After visiting the urinal, they returned to the investigator and described their experiences Each drug was given to ten normal subjects

Results The adrenergic, adrenolytic and antihistaminic agents (ephedrine, regitine, pyribenzamine and benadryl) demonstrated no effect on the cystometrographs of the reflex neurogenic bladders or the voiding ability of the normal subjects despite relatively enormous doses of the drugs

The anticholinergic drugs, atropine and banthine, depressed or abolished the uninhibited contractions of the reflex neurogenic bladders, basic detrusor to-

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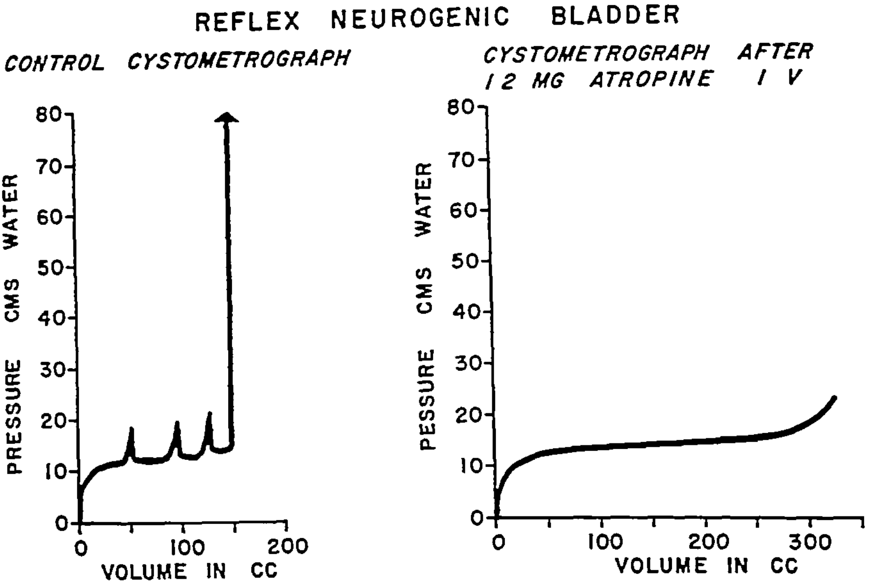

FIG 1 Cystometrographs illustrate ability of atropine to abolish contractions of reflex neurogenic bladder

nicity was not affected Figure 1 depicts a typical reaction to atropine The responses of the normal subjects to 50 mg banthine intravenously included decreased urge to void, difficulty in initiating urination, weak interrupted stream and feeling of incomplete emptying of the bladder

The cholinergic drugs urecholine and neostigmine, produced a change in the function of the reflex paraplegic bladders if they were given in a sufficient dosage In the preliminary testing period it was observed that 5 mg of urecholine or 1 5 mg of neostigmine subcutaneously had no effect on some of the reflex bladders Consequently the dose was doubled for both compounds and responses were elicited regularly The cholinergic drugs stimulate the bladder to contract at a smaller capacity and with greater force, basic vesical tonicity is not affected Figure 2 illustrates the response of a reflex neurogenic bladder to urecholine

When the normal subjects were given the cholinergic compounds, the most common reaction was an increased desire to urinate, in several subjects the desire was uncontrollable It is interesting to note that when the bladder is empty, urecholine does not initiate a desire to urinate Most of the patients did not notice any increased ease or force in urination

Discussion The observations made in the first part of this study demonstrate that drugs altering parasympathetic activity do affect bladder function These findings are entirely in accord with present concepts of bladder physiology[10] which hold that the motor fibers to the bladder are parasympathetic The sympathetic nervous system plays no part in the process of micturition

Ephedrine has been found to be effective by many physicians in decreasing

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After completion of administration of the drugs to the patients with reflex neurogenic bladders, the various compounds with the exception of atropine were tested in subjects with normal bladders, some of these were medical students and house staff The subjects were advised to present themselves to the investigator when they had a strong desire to urinate At this time they were given an injection of one of the drugs and instructed to attempt to empty their bladders within 10–20 minutes After visiting the urinal, they returned to the investigator and described their experiences Each drug was given to ten normal subjects

Results The adrenergic, adrenolytic and antihistaminic agents (ephedrine, regitine, pyribenzamine and benadryl) demonstrated no effect on the cystometrographs of the reflex neurogenic bladders or the voiding ability of the normal subjects despite relatively enormous doses of the drugs

The anticholinergic drugs, atropine and banthine, depressed or abolished the uninhibited contractions of the reflex neurogenic bladders, basic detrusor to-

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[9] Allen, J G Harkins, H N Moyer, C A and Rhoads, J E Surgery Principles and Practice Philadelphia J B Lippincott 1957

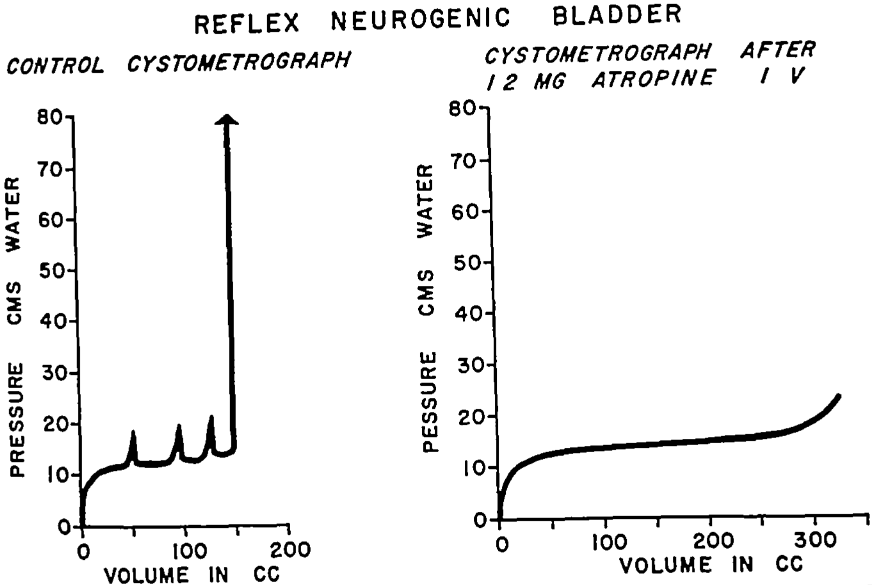

Fig 1 Cystometrographs illustrate ability of atropine to abolish contractions of reflex neurogenic bladder

nicity was not affected Figure 1 depicts a typical reaction to atropine The responses of the normal subjects to 50 mg banthine intravenously included decreased urge to void, difficulty in initiating urination, weak interrupted stream and feeling of incomplete emptying of the bladder

The cholinergic drugs, urecholine and neostigmine, produced a change in the function of the reflex paraplegic bladders if they were given in a sufficient dosage In the preliminary testing period it was observed that 5 mg of urecholine or 1 5 mg of neostigmine subcutaneously had no effect on some of the reflex bladders Consequently the dose was doubled for both compounds and responses were elicited regularly The cholinergic drugs stimulate the bladder to contract at a smaller capacity and with greater force, basic vesical tonicity is not affected Figure 2 illustrates the response of a reflex neurogenic bladder to urecholine

When the normal subjects were given the cholinergic compounds, the most common reaction was an increased desire to urinate, in several subjects the desire was uncontrollable It is interesting to note that when the bladder is empty, urecholine does not initiate a desire to urinate Most of the patients did not notice any increased ease or force in urination

Discussion The observations made in the first part of this study demonstrate that drugs altering parasympathetic activity do affect bladder function These findings are entirely in accord with present concepts of bladder physiology[10] which hold that the motor fibers to the bladder are parasympathetic The sympathetic nervous system plays no part in the process of micturition

Ephedrine has been found to be effective by many physicians in decreasing

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[10] Lapides, J Observations on normal and abnormal bladder physiology J Urol 70 74 1953

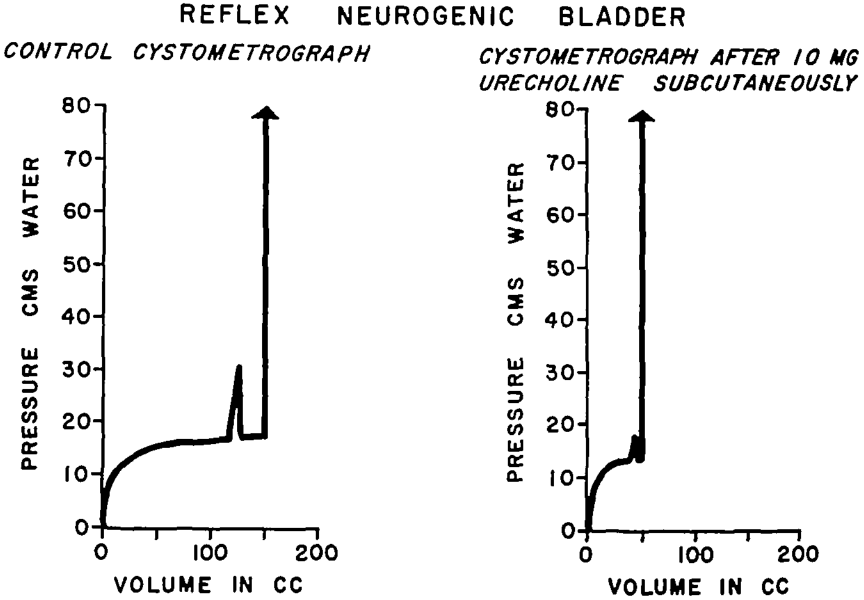

FIG 2 Effect of urecholine in stimulating reflex neurogenic bladder to contract at smaller volume and greater force

nocturnal enuresis in children Some ascribe its effectiveness to stimulation of the internal vesical sphincter by virtue of its adrenergic action, this is pure armchair theorization and is completely contrary to all valid experimental evidence Most physicians now agree that the therapeutic value of ephedrine lies in its ability to make patients sleep less soundly and thus be more aware of a full bladder[11]

The case reports describing urinary complications associated with the use of antihistaminic and adrenolytic drugs discuss patients receiving several medications simultaneously and having multiple complaints Critical analysis of these reports reveals that there is little or no basis for ascribing the urinary complaints to the drug implicated

When administered in a single dose, none of the drugs used in this study (including the cholinergic and anticholinergic compounds) had any influence on the inherent tonicity of bladder muscle This property of bladder muscle is similar to the response of ureteral smooth muscle to drugs[12]

PART 2

Because banthine impairs the transmission of motor impulses through parasympathetic ganglia and neuromuscular junctions, it is being used to control bladders with uninhibited contractions due to lesions of the cortico-regulatory tract Such bladders are observed in patients with multiple sclerosis, following cerebrovascular accidents, neurogenic enuresis in children, etc Banthine has been effective also in enlarging the capacity of spastic bladders For a complete account of the uses of banthine in urological disturbances, the reader is referred to a previous report [13]

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[11] Roland, S I Essential nocturnal enuresis treated with D amphetamine sulfate J Urol, 71 216, 1954

[12] Lapides, J The physiology of the intact human ureter J Urol 59 501, 1948

Prior to this investigation urecholine had been used at the University of Michigan Medical Center but had been discarded because of its apparent ineffectiveness The present experiments, involving the use of urecholine in patients with reflex neurogenic bladders, indicate that high doses of the drug are necessary for appropriate stimulation of the bladder In fact, the usual adequate dose has been found to be 10 mg subcutaneously or 50 mg orally, these quantities are at least twice the usual recommended amount [14] No dangerous reactions to these dosages were noted in any of the patients tested to date If the side-effects are unusually disagreeable to a particular patient, the symptoms can be terminated abruptly with the intravenous administration of 50–100 mg banthine

Urecholine has been used successfully in a variety of situations involving difficulty in emptying the urinary bladder not due to physical obstruction, e g postoperative urinary retention,[15 17] neurogenic dysfunction[15] and decompensated atonic bladders [16] We have found the drug to be effective in correcting urinary dysfunction due to tabes (sensory paralytic bladder), advanced multiple sclerosis, post-spinal cord operations, postpartum atonicity, reflex neurogenic bladders temporarily impaired by systemic illness and atonicity associated with prostatism following prostatectomy

In treating patients with the cholinergic agents it has been noted that the drugs have two properties One quality involves their parasympathomimetic activity which is readily evident after the administration of one adequate dose and which has been described in many reports The other characteristic has been less well recognized and involves the ability of these drugs to alter the function of the muscle cells of the bladder To observe this property one must administer the cholinergic agents over a prolonged period of time No ready explanation can be offered as to the mechanism of this characteristic, it must await investigations by the cellular physiologists

Two cases are presented to illustrate the effect of prolonged cholinergic therapy on the atonic bladder J M , an elderly white man, was admitted to the hospital August 26, 1956, in complete urinary retention Examination revealed an enlarged prostate and a residual urine of 2500 cc Retropubic prostatectomy was performed September 10 The urethral catheter was removed on the sixth postoperative day and the patient voided in 250 cc amounts A check for residual urine on the tenth postoperative day revealed it to be 500 cc The patient was put back on intermittent urethral catheter drainage over a period of four weeks Trials off catheter during this time revealed the patient to be carrying urinary residuals varying between 500–800 cc He was placed on urecholine 10 mg subcutaneously t i d for three days A check for residual urine at this time demonstrated 30 cc in the bladder The urecholine was discontinued for several days and a repeat catheterization indicated the residual urine had increased to 800 cc Therefore, the patient was given urecholine (10 mg subcutaneously t i d) again for a period of three days, this reduced the residual urine to 10 cc The medication was changed then to the oral form in a dose of 20 mg t i d and the residual urine again increased to 600 cc Changing the oral dose of urecholine to 50 mg t i d brought the residual urine to within normal limits The patient received the increased oral dosage of urecholine for a week and then was allowed to remain off the drug for another week A check for residual urine at this time revealed 325 cc The patient was put back on the 50 mg dose of urecholine again and the residual urine was reduced to 30 cc He remained on the drug for three more weeks Discontinuation of the urecholine at this time did not result in a high residual urine The patient has been voiding normally with no residual urine for the past seven months

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[13] Lapides J and Dodson A I , Jr Observations on effect of methantheline (banthine) bromide in urological disturbances Arch Surg , 66 1 1953

[14] Council on Pharmacy and Chemistry Use of bethanechol chloride for paralytic ileus and urinary retention after ganglionic blockade J A M A , 162 731 1957

[15] Starr I and Ferguson L K B methylcholine urethane Its action in various normal and abnormal conditions especially postoperative urinary retention Am J Med Sc , 200 372 1940

[16] Lee W L The clinical use of urecholine in dysfunctions of the bladder J Urol , 62 300 1949

[17] Garvey F K Bowman M C and Alsobrook, W L The use of beta methylcholine urethane in postoperative urinary retention Surg , Gynec & Obst , 88 196, 1949

The second case involved a 34-year-old man who was admitted to the hospital in complete urinary retention Investigation revealed the patient to have tabes dorsalis with a sensory paralytic bladder He was placed on dependent catheter drainage for a week during which time he received antiluetic therapy A trial off catheter on a two-hour voiding schedule revealed the patient to have great difficulty in urinating and to be carrying a residual of 1,000 cc Dependent bladder drainage was reinstituted for another week A repeat trial of voiding indicated the patient to be still carrying a large residual urine Therapy with urecholine was initiated but then changed to neostigmine when the supply of urecholine ran out The patient was given 2 0 mg of neostigmine subcutaneously every four hours for a period of 2½ weeks During this time intermittent catheterization revealed a gradual reduction in residual urine to 10 cc after 12 days When the neostigmine was stopped, the patient continued to void well without an abnormal residual of urine in the bladder

On our service both of the patients discussed would have been placed on suprapubic cystostomy drainage prior to the present investigation of the cholinergic drugs And they would have been kept on drainage until they demonstrated satisfactory emptying of their bladders, this might have involved months The observation that atonic bladders can be benefited by prolonged cholinergic therapy has been made previously by Starr,[15] Lee[16] and Dodson [18] *The point to be emphasized about urecholine therapy is that the medication must be given in an adequate dose* It is true that younger individuals are more sensitive to urecholine than the older age group and may require a smaller dose than 10 mg subcutaneously It is believed, however, that the full dose should be given initially to all adults and not lowered unless side-reactions are too marked With the dosage advocated all patients will demonstrate sweating, lacrimation and perhaps some gastrointestinal complaints, these symptoms are less prominent on the oral form of urecholine A few days of discomfort for the patient on the parenteral form of urecholine is a small price to pay for the avoidance of an operation and months of urinary drainage Incidentally, urecholine has been used in preference to other cholinergic agents because it is said to have the widest margin of safety of the most potent cholinergic drugs

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[18] Dodson, A I and Gilbert, D R A comparative study of the effects of parasympathetico mimetic drugs on the urinary bladder South Surg , 16 812, 1950

The following regimen of urecholine therapy has been found to be very satisfactory Initially the patient is placed on 10 mg of urecholine subcutaneously t i d The parenteral form of therapy is continued for 2–3 days If the patient appears to respond to the treatment, the oral urecholine is substituted for the parenteral form The oral dose is 50 mg t i d At the start of therapy the patient should be catheterized for residual urine every 24–48 hours A trial of voiding without urecholine therapy can be made when the patient has had a residual urine of 30 cc or less for five days If the patient demonstrates too great a response to 10 mg of urecholine subcutaneously, then the dose can be reduced to 7 mg Most of the patients can tolerate the 50 mg oral dose without difficulty

CONCLUSIONS

Adrenolytic, adrenergic and antihistaminic substances have no effect on urinary bladder or sphincter function

The anticholinergic drugs (atropine, banthine) block transmission of motor impulses to the bladder and thus tend to inhibit detrusor activity

The cholinergic drugs (urecholine, neostigmine) accentuate the effect of the motor impulses on the detrusor and cause increased voiding contractions

None of the drugs tested in a single dose had any effect on inherent bladder tonicity

Clinically, banthine can be used to control bladders with uninhibited contractions

Urecholine in practice is very effective in initiating micturition and reducing residual urine in a variety of nonobstructive urinary disturbances provided the drug is given in an adequate amount for an appropriate period of time

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FURTHER OBSERVATIONS ON EXCRETORY CYSTOMETRY

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In a previous study performed upon spinal cord injury patients, the results of retrograde and excretory cystometry were compared The following observations were made upon upper motor neuron bladders 1) Truer (higher) capacity values were disclosed with the excretory rather than with the retrograde method, 2) the base line, indicating detrusor tone, was higher as a rule with the retrograde method than with the excretory method, 3) the ability of the detrusor to eject the catheter was greater with the retrograde method, tending to mislead by showing seemingly better bladder function than the excretory method, 4) in patients with lesions above the visceral sympathetic outflow, the retrograde method elicited a hypertensive blood pressure response at lower volumes than the excretory method The following observations were made upon lower motor neuron bladders There were no marked differences in either method of cystometry in regard to capacity, detrusor tone or bladder balance

Since only a few patients of the original study were catheter-free at the time of the report, the purpose of this study was to follow a group of patients for a longer period of time in order to 1) learn what pattern relationships existed between retrograde and excretory cystometry, 2) learn what the pattern relationships were just prior to becoming catheter-free as a method of better prognosticating the future of an imbalanced bladder, 3) learn if excretory cystometry is of value among hypocapacity bladders, 4) learn if permitting the bladder to fill up to 1000 cc during a two-hour excretory cystometry period will prevent automaticity because of overdistention, and 5) learn how the catheter-free states were obtained and the length of time required

MATERIAL AND METHODS

Fifty-two patients with traumatic cord lesions were studied Forty-eight patients had upper motor neuron bladders, whereas four had lower motor neuron bladders Among the upper motor neuron bladders were eighteen complete cervical lesions, eight incomplete cervical lesions, two complete thoracic 1–6 lesions, two incomplete thoracic 1–6 lesions, nine complete thoracic 7–12 lesions, three incomplete thoracic 7–12 lesions, five complete lumbar lesions and one incomplete lumbar lesion Among the lower motor neuron bladders were one complete thoracic 8 lesion, two complete lumbar lesions, and one incomplete lumbar lesion

None of the patients studied were in spinal shock

Excretory cystometry was usually performed first, followed by retrograde cystometry within 1–4 days later Both methods were performed routinely every 3–4 weeks with exceptions due to illness, uncooperativeness on the part of the patient or cancellations due to other emergency work

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Technique of performing cystometry was as follows

Retrograde cystometry was performed using a size 20 whistle tip catheter after the bladder had been emptied The Y tube was attached to the catheter, from one limb of the Y tube, the tubing led to the Lewis cystometer Through the other limb of the Y tube, distilled water at room temperature entered in a continuous flow at the rate of 25 cc per minute This instillation was terminated either by a detrusor contraction which ejected the catheter, autonomic hyperreflexia, manifested by blood pressure hypertension or at a volume of 400 cc

Excretory cystometry with a whistle tip catheter was performed as follows The patient was instructed to drink one glass of water hourly from 6 00 a m until the scheduled time for cystometry The fluid intake was continued during cystometry A size 20 whistle tip urethral catheter was gently introduced and the bladder was emptied Strain, Credé, or other extrinsic methods were not used to empty the bladder since this might set off reflex activity With its tip in the bladder the catheter was then connected to the Lewis cystometer in the usual manner The intravesical volume was supplied by the patient's excreted urine Sufficient time was allowed for stabilization before the investigation was started in order to avoid the recording of responses caused by such stimuli as change of catheters, moving the patient to the testing room, transferring the patient from the guerney to the cystoscopy table, and the like (The procedure should be preferably done at the bedside) Cystometry was continued until the catheter was ejected, but it was terminated after two hours, if the catheter was ejected by a voiding contraction of the detrusor, or if a hypertensive autonomic response was noted

RESULTS

Four hundred cubic centimeters were accepted as normal capacity in this study

One hundred three retrograde and excretory cystometry combinations were reviewed among the patients with upper motor neuron bladders The following patterns were observed 28 showed capacities below 400 cc in both types of cystometry, 27 showed capacities below 400 cc with retrograde cystometry and capacities above 400 cc with excretory cystometry, 48 showed capacities above 400 cc in both types of cystometry Included in these patterns are also those patients with autonomic hyperreflexia Only one pattern was found among the lower motor neuron bladders, namely, capacities above 400 cc in both types

The following capacity patterns of retrograde and excretory cystometry were found among 23 patients with upper motor neurons just prior to becoming catheter-free Nine patients showed capacities below 400 cc with retrograde and excretory cystometry Ten patients showed capacities below 400 cc with retrograde and above 400 cc with excretory cystometry The patterns of eight patients were unknown Prior to becoming catheter-free, the patients with lower motor neuron bladders showed hypercapacity in both the retrograde and excretory methods

The tests showed that in the group of patients with a capacity below 400 cc, with both retrograde and excretory cystometry, in all except one instance the capacity was greater with excretory cystometry, this difference in capacity ranged from 30 cc to 290 cc

Twelve of the 31 patients became automatic despite the elevated capacities which were found at one time or another during the routine testing of two hour excretory cystometry The capacities ranged from above 400 cc to over 1000 cc

Among the group of patients with upper motor neuron bladders 17 became catheter-free spontaneously within four to 26 months following injury Ten patients became catheter-free following various blocking procedures within five to 24 months Four patients became catheter-free by means of transurethral resection within 11 to 30 months

Among the lower motor neuron bladders 2 patients became catheter-free spontaneously three and six months after injury One patient became catheter-free 11 months after injury by means of transurethral resection

Completeness or incompleteness of the spinal cord lesion did not seem to play a role in this series of cases

DISCUSSION

Obviously, the patterns found depended on the time since injury During spinal shock hypercapacity with hypotonicity of the detrusor is anticipated The ice water test of Bors will indicate when the autonomic innervation of the bladder is out of shock, despite a positive ice water test many of the cases in this series displayed hypercapacity and hypotonicity of the detrusor with both types of cystometry This only shows that the stimulus of an extrinsic (distilled water) or intrinsic (urine) increment is far smaller than that of the ice water This study has furthermore again shown that upper motor neuron bladders in patients with similar neurological levels will not necessarily follow a comparable pattern on cystometry Many imbalanced bladders will show a hypocapacity soon after spinal shock has disappeared and this will persist for indefinite periods with both types of cystometry, per contra, other patients will show hypercapacity for indefinite periods For example, in this group there was a patient with a complete cervical lesion who had hypocapacity with both types of cystometry for over two years and remained imbalanced, whereas another patient with a comparable level showed hypercapacity for over three years and also remained imbalanced

This study verifies the fact that upper motor neuron bladders show less capacity with the retrograde than with the excretory method This appears quite understandable because the retrogradely instilled water acts as a more powerful and quick stroke of the reflex hammer in eliciting the bladder jerk than does the gradual and more physiologic increment of the excreted urine This marked difference in capacity is absent in patients with lower motor neuron bladders Since truer capacities are found with excretory cystometry, spinal anesthesia has become less important in order to test bladder capacities Although truer capacities can be obtained with excretory than with retrograde methods, the physiologic capacity, unimpeded by the stimulus of the indwelling catheter, can be determined only at the bedside when the urinary residual is tested

Although it is known that bladder changes may occur from day thought that adequate results could be obtained if excretory a cystometrics were done three to four weeks apart

Fourteen of the 31 catheter-free patients showed hypocapacity w and hypercapacity with excretory just prior to developing reflex of the 31 patients showed hypocapacity with both methods, althou 31 patients showed hypercapacity with both methods, these result utilized for devious reasons, if one wanted to be accurate The t apparent, namely, the patients with upper motor neuron bladders hypocapacity with the retrograde cystometry became catheter-fr

It must be re-emphasized that while cystometry is a valuabl must compare its findings with the results of the capacity-residua performed without a catheter and at the bedside The importance stimulus is illustrated by the example of a patient with a complete of 27 months' duration In spite of hypocapacity with both types which has not changed since the onset, he displays hypercapacity residual test

Each bladder will develop its own "intrinsic physiologic capacit we have no control One patient in this series displayed a 55 cc retrograde and an 85 cc capacity with excretory cystometry, yet catheter-free state reveals a 580 cc capacity Another patient sl capacity with both types of cystometry, his balanced automatic b a capacity of 240 cc Therefore, it is incorrect to presume, as many balanced reflex bladders show hypocapacity, per contra, true lower bladders show hypercapacity with all methods of study

Although hypocapacity may be present with both retrograde cystometry, relatively larger capacities are found with the excr This is important for the prescription of drugs which could be ill relied exclusively on retrograde cystometry

The question of time has arisen, are two hours too long a perio cystometry because of possible overdistention? This can be refute tions that 1) even then when a one-hour bedside residual was test were found, the bladder function became nevertheless reflex, and t which ranged from 600 cc to 1000 cc during excretory cystometry d the development of reflex function To perform a two-hour resid imbalanced bladder at the bedside without a catheter would pro gerous because of overdistention, but two-hour excretory cysto haps less dangerous since the ejection of the catheter indicates to t empty the bladder immediately

The values of overdistention are relative and depend on the pa of the neurogenic bladder, a volume of 400 cc may be overdistent the intrinsic capacity but a volume of 900 cc is not overdistention at that stage is 1500 cc However, since we cannot know or pr capacity at any particular period, it is advisable not to exceed a vo spontaneously, 10 by means of various blocking procedures, and 4 by transurethral resection It is interesting that only four required surgery whereas 27 became automatic with conservative care within four to 26 months Yet, as late as 30 months after injury, transurethral resection rendered one bladder automatic It is noteworthy that these bladders became automatic without bladder training or tidal drainage

SUMMARY

Fifty-two patients with traumatic cord lesions were submitted to both retrograde and excretory cystometry

The value of excretory cystometry, as reported originally and enumerated in the introductory remarks, has proven to be valid also in a larger number of cases

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STUDIES OF THE NATURE OF PAROXYSMAL HYPERTENSION IN PARAPLEGICS

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In 1917 Head and Riddoch, in their classical study of World War I paraplegics, described paroxysmal hyperactive autonomic reflexes occurring with bladder distention in those patients with lesions in the high dorsal or cervical cord

Subsequent investigations have shown that paroxysmal hypertension occurs in at least 85 per cent (Bors) of paraplegics with lesions above the level of D5 It is produced most regularly by bladder distention, but bowel distension, or a variety of other stimuli below the level of the lesion can likewise precipitate an attack For paroxysmal hypertension to occur the lesion must be above the major splanchnic outflow The usual lowest lesion has thus been at D5 although levels of D6 and D7 have been reported (Schumacher and Guthrie)

The reaction in the autonomic nervous system is analogous to somatic hyperreflexia in which severe striated muscle spasms occur because of interruption by transverse myelitis of regulatory pathways from higher centers

The authors became interested in this problem in April 1956 when consultation was requested to evaluate the urinary status of a paraplegic at the Ann Arbor Veterans Hospital This 21-year-old boy (FW AAVAH 13507) had sustained a fracture dislocation of C4 on C5 in an automobile accident four months prior to admission At that time a laminectomy disclosed severe damage to the right side of the cord and contusions of the left

When first seen by the consultant the patient was complaining bitterly of a headache Physical examination showed profuse sweating, patchy erythema, and goose pimples over the face, arms, and upper chest The blood pressure was found to be 230/140 with a pulse rate of 40 The bladder was distended Decompression of the bladder resulted in an immediate disappearance of all of the signs and symptoms with a return of the blood pressure to normotensive levels

The present belief is that this reaction represents an uncontrolled sympathetic outflow The present study was conducted in an effort to determine the parts played by the sympathetic nervous system and the adrenals in the production of paroxysmal hypertension Renal hemodynamics were also investigated in one patient who underwent urinary ileostomy

MATERIALS AND METHODS

The subjects were eight very co-operative paraplegics All of their lesions were between C5 and D1, and all were traumatic in origin Bladder distention was used to produce paroxysmal hypertension Rectal distention and peripheral stimuli were found to be unreliable or unworkable

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Read at annual meeting of North Central Section of American Urological Association, Mackinac Island Mich August 29-31 1957

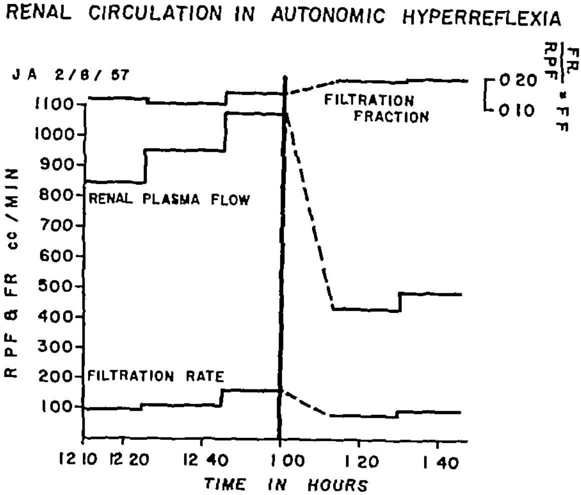

FIG 1 Hypertension was produced at 1 00 p m Renal plasma flow was measured by PAH excretion Filtration rate was determined by inulin excretion

The patients were placed on urethral catheter and their bladders distended with fluid until hypertension was produced * Serial blood pressures and pulses were taken at 30 second intervals in six patients while the polygraph was used in two subjects When a hypertensive plateau was established, drugs were injected parenterally in an effort to reduce the blood pressure The drugs used were the adrenolytic agents regitine (5 and 10 mg intravenously) and benodaine (20 mg intravenously) and the ganglionic blocking agent hexamethonium (25 mg intravenously)

The urinary excretion of the breakdown products of adrenalin and noradrenalin, catechol amines was measured in seven patients Urines were collected before, during, and after episodes of paroxysmal hypertension Catechol amines were measured by the fluorescent techniques of Von Euler and Weil-Malherbe

Renal plasma flow, measured by PAH, clearance, and glomerular filtration rate, estimated by inulin clearance, were used to determine changes in renal dynamics during the hypertensive episode in one patient with a urinary ileostomy Renal studies were not done on the other paraplegics because it was not possible to distend the bladder to produce the hypertension and simultaneously collect urine for clearance determinations

RESULTS

The adrenolytic agents, benodaine and regitine, had no effect on the blood pressure, or sweating, flushing, and headache occurring during the hypertensive episode in any of the patients The urinary excretion of catechol amines was unchanged during the periods of elevated blood pressure †

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* The rate of filling made no difference in the response so about 150 drops per minute was used

† All baselines were within the normal 10 to 100 micrograms per 24 hours and minor fluctuations occurred within this range during hypertension

Hexamethonium, the ganglionic blocking agent, however, lowered the blood pressure to normal levels and relieved the signs and symptoms in all of the paraplegics

The renal function studies (fig 1) demonstrated a marked decrease in renal plasma flow and glomerular filtration rate during paroxysmal hypertension in the one patient studied *

CONCLUSIONS

The results of these studies indicate that the sympathetic nervous system plays the primary role in the production and maintainance of paroxysmal hypertension in paraplegics This finding is in accord with the studies of Kurnick, Thompson and Witham, and Schumacher and Guthrie The adrenals apparently do not participate in the hyperactive autonomic response The kidney function studies demonstrate indirectly the vasoconstriction of the renal vessels during the hypertensive period

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* Because of anatomically inherent technical difficulties in the collection of specimens fine interpretation of hemodynamics is disallowed

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SPINAL CORD INJURY EARLY UROLOGICAL TREATMENT

GEORGE C PRATHER

The urological program immediately following spinal cord injury is somewhat standardized at present and I offer nothing new The time period covered by my paper begins within twelve hours after injury and continues for at least six months in those who have a severe injury The procedures which are not infrequently required for ultimate optimum rehabilitation at a later period of recovery will be described by others in this symposium

It is during the early period after spinal cord injury that we endeavor to protect the urinary tract from complications and thus try to facilitate maximum physiological recovery In our efforts to protect the urinary apparatus from conditions prone to those incapacitated by paralysis, and from errors or accidents which can so easily be produced by misunderstanding the principles and techniques involved, we naturally should think of the whole urinary tract We should strive to prevent stone formation and infection in the kidneys We should be aware of vesicoureteral reflux if it is present in order to avoid any form of bladder program that might contribute to renal woes We should care for the bladder in a manner which will attempt to avoid stone formation, intramural infection or adverse change in capacity We should take every possible precaution to prevent urethral complications which delay maximum recovery Thus, each and every time we see our paraplegic patient we try to visualize the status and condition of the whole urinary tract, even though at times it seems impossible to understand the details of the various physiological processes which are taking place or fail to take place

Now, to transfer from the idealistic picture to the practical program, our immediate objective is to place the bladder on drainage and obtain certain base line data as soon as the general condition of the patient permits

A 16F soft rubber balloon catheter seems best in size and type for the average adult After sterile catheterization, in order to empty all of the urine from the bladder, the catheter can be connected to a sterile closed drainage and irrigation system to permit periodic manual irrigation of the bladder every four hours, using 100–150 cc physiological saline solution for an irrigating medium This will produce a cleansing action and after a fashion simulate at least a transient, partial distention of the bladder Why saline as an irrigating solution? It is nonirritating and I do not know of a better medium for routine use

Shortly one can consider the desirability of some form of tidal drainage If proper equipment and proper personnel are at hand I believe the automatic system may be used with satisfaction, although personally I have never been convinced that true tidal drainage is necessarily contributory toward maximum recovery of bladder function

If it is necessary to devise some type of tidal apparatus and if the attendants

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Read at annual meeting of American Association of Genito Urinary Surgeons, Hot Springs, Va May 1-3, 1957 are not familiar with the intricacies and caprices of this system, I deem it far safer to rely on the simple closed system with manual control of irrigation

Certainly in civilian life, one should not go directly to suprapubic cystotomy The extent of the spinal cord injury cannot be immediately foretold The patient may have considerable systemic shock There may be considerable abdominal distention from ileus The neurosurgeon may be busy with spinal punctures or surgical procedures A catheter will drain the urine effectively and a clean bladder can be maintained without the additional risk of a surgical procedure

Although now well known, it seems wise to stress the use of a soft and small urethral catheter Just as pressure on the skin over bony prominences of a paralyzed person quickly leads to necrosis in that area, a too large or a too rigid catheter no doubt will contribute to pressure necrosis at the penoscrotal angle, a periurethral abscess, urethral fistula and perhaps urethral diverticulum If the proponents of catheter drainage in the paraplegic patient are to win over those who favor suprapubic drainage, urethral and scrotal sepsis must be kept at a very low incidence Great care with sterility at the time of catheterization or change of catheters, and the smallness and softness of the catheter will help to avoid distressing complications

One often reads "the catheter should be changed every seven to ten days" That may be good advice if there is a tendency toward encrustation However, I prefer individual consideration of said catheter, leaving it in place as long as it appears to drain and irrigate efficiently If a catheter will function properly for two to three weeks, let us avoid more frequent manipulation Should a catheter be left in place without changing for longer than perhaps three weeks? Probably not, because of the tendency for eggshell-like stone deposit to form on the outside of the balloon part of the catheter in some individuals

Let us assume that the patient has survived the initial stress and shock of his accident and that a few weeks have gone by It is time now to think of obtaining base line data in regard to the urinary tract, information which will be extremely helpful in the diagnosis and treatment of problems in the future

Information most desired is degree of tone and extent of detrusor activity if present, presence or absence of ureterovesical reflux, and the status of the upper urinary tract

The much debated cystometric determination needs discussion All will agree that individual determinations can be difficult to explain or classify and yet it is probably our best method of estimating the presence or absence of detrusor activity and tone The examination will not tell the examiner which patient will be able to void because there are other factors in the region of the bladder neck and external sphincter muscle which have importance in the act of urination However, the test should indicate which bladders have a chance of performing with reasonable efficiency if obstructive elements are not an impediment

Cystometrograms—serial in a sense—done by the same person and with the same technique every two to three weeks are likely to be more informative than one single examination It is the change or evidence of return of detrusor activity which leads to encouragement and elation Likewise continued hypotonicity

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SPINAL CORD INJURY EARLY UROLOGICAL TREATMENT

GEORGE C PRATHER

The urological program immediately following spinal cord injury is somewhat standardized at present and I offer nothing new The time period covered by my paper begins within twelve hours after injury and continues for at least six months in those who have a severe injury The procedures which are not infrequently required for ultimate optimum rehabilitation at a later period of recovery will be described by others in this symposium

It is during the early period after spinal cord injury that we endeavor to protect the urinary tract from complications and thus try to facilitate maximum physiological recovery In our efforts to protect the urinary apparatus from conditions prone to those incapacitated by paralysis, and from errors or accidents which can so easily be produced by misunderstanding the principles and techniques involved, we naturally should think of the whole urinary tract We should strive to prevent stone formation and infection in the kidneys We should be aware of vesicoureteral reflux if it is present in order to avoid any form of bladder program that might contribute to renal woes We should care for the bladder in a manner which will attempt to avoid stone formation, intramural infection or adverse change in capacity We should take every possible precaution to prevent urethral complications which delay maximum recovery Thus, each and every time we see our paraplegic patient we try to visualize the status and condition of the whole urinary tract, even though at times it seems impossible to understand the details of the various physiological processes which are taking place or fail to take place

Now, to transfer from the idealistic picture to the practical program, our immediate objective is to place the bladder on drainage and obtain certain base line data as soon as the general condition of the patient permits

A 16F soft rubber balloon catheter seems best in size and type for the average adult After sterile catheterization, in order to empty all of the urine from the bladder, the catheter can be connected to a sterile closed drainage and irrigation system to permit periodic manual irrigation of the bladder every four hours, using 100–150 cc physiological saline solution for an irrigating medium This will produce a cleansing action and after a fashion simulate at least a transient, partial distention of the bladder Why saline as an irrigating solution? It is nonirritating and I do not know of a better medium for routine use

Shortly one can consider the desirability of some form of tidal drainage If proper equipment and proper personnel are at hand I believe the automatic system may be used with satisfaction, although personally I have never been convinced that true tidal drainage is necessarily contributory toward maximum recovery of bladder function

If it is necessary to devise some type of tidal apparatus and if the attendants

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Cystometrograms—serial in a sense—done by the same person and with the same technique every two to three weeks are likely to be more informative than one single examination It is the change or evidence of return of detrusor activity which leads to encouragement and elation Likewise continued hypotonicity indicates that immediate rehabilitation may not be at hand Therefore, let us stress periodic cystometrograms as important documents in the program for proper care of the paraplegic bladder

In performing cystometric study, I prefer the constant drip (about 100 drops per minute) water manometer type of study The examiner, constantly observing the level and variations in the manometer during the test and watching the patient as a whole, has a far better idea of bladder action than the one who simply reviews a recording or a chart made by someone else Likewise a constant drip filling of the bladder will be more physiological than adding fluid by 50 cc increments

Base line information concerning the question of ureterovesical reflux and the anatomical condition of the upper urinary tract can be obtained on one trip to the x-ray department Following a plain film of the urinary tract a cystogram is done, using a volume of opaque medium to the point of reflex activity of the bladder if detrusor activity is present or up to 300 cc if the bladder is hypotonic These films will demonstrate reflux up the ureters if it is present After the cystographic medium has been emptied from the bladder, an intravenous urogram can be done for delineation of the upper urinary tract

Thus, in the first few weeks after spinal cord injury, basic data pertaining to the urinary tract have been obtained This information will be valuable to compare with the findings at subsequent examinations

Because infection and stone formation in the urinary tract are two major hazards in the life of the paraplegic patient, what can we do to keep these complications at a minimum?

Let us mention urinary tract infection first I believe that it is impossible to keep the bladder bacteria-free with a catheter in place A thick purulent urinary condition can usually be avoided however by diligent care of the tidal or manual irrigations of the bladder

We wish to avoid renal infection if possible or avoid major involvement if present There are many points of view as to the best way to accomplish this—none of them probably infallible The following is a personal opinion in regard to the program which will cover some months Firstly, I would not use sulfonamide or antibiotic medication as a routine prophylactic measure as long as there are no clinical indications of pyelonephritis If a febrile episode develops which appears to be caused by renal infection, I would suggest a broad spectrum antibiotic without delay for at least a week If response to this medication has been satisfactory it would then seem reasonable to use a daily maintenance dose (usually one quarter to one half the routine daily quantity for acute pyelonephritis) of either an antibiotic or sulfonamide for an indefinite period Experience with this type of program has seemed to permit an afebrile course over a long period more effectively than a plan in which all medication is stopped when an acute episode appears to be over While it is true that further febrile periods of renal infection may develop at which time full dosage therapy may be required, I favor a continued maintenance policy in the paraplegic or others who seem to be prone to pyelonephritis

Our next consideration is the threat of stone formation in the kidneys Known prophylactic measures are firstly, frequent changes in body positions and early ambulation and secondly, a large daily urinary output

The dietary regimen is difficult to evaluate as it relates to stone formation, but the paraplegic patient sometimes has serious over-all metabolic problems which must be seriously considered without regard for the urinary tract Measures need to be taken to minimize the wasting of body tissue All essential nutrients are required with emphasis on proteins and a high total caloric intake Thus the general problem of nutrition takes precedence over any possible effect on urinary stone formation Aluminum gels will add to the difficulties of a sluggish intestinal tract Daily intake of salicylates is yet to be finally evaluated in the role of a stone deterrent

Thus, a brief outline of a program for the care of the urinary tract during the early stages of recovery following spinal cord injury has been presented My comments represent personal opinion, not universal agreement Future progress in this field will be received with heartfelt thanks both by the patient and the urologist I look forward to other papers in this symposium which deal with the problems of late or definitive rehabilitation of the urinary tract

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TREATMENT OF THE CHRONIC PHASE OF CORD BLADDER

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I propose to discuss the management of patients in whom acceptable function of the bladder has not developed as a result of conservative treatment and education in respect to the bladder Mr Norman Gibbon tells me that approximately 25 per cent of the paraplegic patients on the service at Southport Paraplegic Center are of this group Talbot suggested the same figure Comarr (1957) was more pessimistic He reported that of 180 paraplegic patients only 36 (20 per cent) became catheter-free as a result of conservative treatment with either straight or tidal drainage and training of the bladder At any rate, we all know that there are plenty of patients in this category who need help This discussion will not be limited to traumatic paraplegia, but will also include "medical" lesions of the central nervous system which confront the urologist in private practice

The three main problems of the chronic phase of cord bladder are 1) persistence of substantial amounts of residual urine, 2) lack of socially acceptable urinary control, and 3) vesicoureteral reflux, with deterioration of the upper part of the urinary tract (which occurs in 25 to 50 per cent of paraplegic persons) I shall briefly discuss the first two Dr Bunts will discuss the third

LOWER MOTOR NEURON LESIONS

Broadly speaking, the so-called spastic urinary tract of the *upper motor neuron lesion* causes the most trouble The so-called flaccid urinary tract of the *lower motor neuron lesion* gives the least trouble and is more amenable to treatment As a dramatic example of the latter statement, I refer you to the published experiences of Dr Collin S MacCarty concerning "selective cordectomy " For the purpose of eliminating severe disabling contractures of the lower extremities in completely paraplegic persons who had lesions in the middle or high thoracic part of the spinal cord which made nursing care difficult, he removed the entire cord below the level of the lesion This of course converted the condition from an upper to a lower motor neuron lesion The postoperative urologic status of those patients was interesting Most had very satisfactory vesical function They were able to void at will every three to five hours with abdominal straining or manual Credé expression, or both, they could empty the bladder completely and with little or no leakage of urine between voidings, unless they were engaging in some strenuous exercise involving marked straining with a moderately full bladder In a few cases, transurethral resection of the vesical neck was necessary to accomplish this result

How does one explain this satisfactory vesical function? Apparently, the denervated external sphincter and vesical neck have enough passive resistance to prevent leakage of urine—and yet are weak enough to allow complete evacuation of urine with straining and manual Credé expression It is now generally agreed

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Read at annual meeting of American Association of Genito-Urinary Surgeons, Hot Springs, Va May 1–3, 1957 that the cord bladder of the lower motor neuron lesion lies exclusively in the province of transurethral resection Nerve blocks and sections are not indicated, for all nerves serving vesical function should be paralyzed (except in unusual cases in which "spotty"—mixed—or incomplete lesions are present) When necessary, transurethral resection should give good results in a high percentage of cases So far as this paper is concerned, it should be remembered that we are using Bors' criteria to prove a lower motor neuron lesion, namely, a relaxed anal sphincter and absent bulbocavernosus and anal reflexes

UPPER MOTOR NEURON LESIONS

Let us now turn our attention to the so-called spastic urinary tract of the upper motor neuron lesion Spasticity (and accompanying hypertrophy) may involve any or all of the following structures 1) detrusor musculature, 2) vesical neck, 3) prostatic urethra, and 4) the external urethral sphincter What is the cause of this spasticity? *In the (striated) external sphincter* it is the typical response of striated muscle to an upper motor neuron lesion and can, of course, vary in degree of severity *In the presence of involvement of the detrusor musculature, vesical neck, and prostatic urethra,* the smooth-muscle component of these structures apparently is affected by abnormal, pathologic stimuli originating in the sacral part of the spinal cord which probably result from lack of control of higher centers Moreover, these impulses may be "aided and abetted" and increased in frequency and irregularity by reflex stimulation from spastic muscles of the perineum and lower extremities

There is still another factor involved It has been shown clinically by Bors and associates and anatomically by Beneventi and Marshall that striated muscle fibers arising from the external sphincter are intertwined with the smooth muscle of the prostatic urethra and vesical neck (especially the anterior half) These striated muscle fibers of course would take part in the spasticity, for the same reason as that given for the external sphincter

TREATMENT

The chief aim in treatment is to reduce or to eliminate spasticity and hypertonicity of the detrusor musculature, vesical neck, prostatic urethra and external urethral sphincter Therapeutic procedures which are available include 1) transurethral resection (of both the vesical neck and prostatic urethra), 2) nerve sectioning (section of the pudendal nerve and Meirowsky's differential sacral neurotomy), 3) subarachnoid injection of alcohol (Sheldon and Bors) or selective cordectomy (MacCarty) and 4) denervation of the bladder by section of the pelvic nerves (nervi erigentes) as described by Leadbetter and Shaffer (1955) These various procedures should be considered complementary rather than competitive For instance, a combination of transurethral resection and nerve block often will accomplish better results than either procedure used alone

How can one decide which procedure to use in a given case? The first step in making such a decision is to analyze just what each procedure can be expected to accomplish Let us briefly consider each procedure from this point of view

Subarachnoid injection of alcohol, selective cordectomy These are "radical" procedures which will completely convert an upper motor neuron lesion to a lower motor neuron lesion (including production of complete, flaccid paralysis of the lower extremities) The procedures of course would be used only in the presence of complete, permanent lesions in which there is no hope of recovery for the cord, and usually as a last resort when other procedures have failed These procedures are especially indicated for patients who have troublesome spastic contractures of the lower extremities which greatly complicate nursing care As previously mentioned under the heading of "lower motor neuron lesions," transurethral resection also will be necessary in some cases, depending upon the degree of muscular hypertrophy or fibrosis which has developed at the vesical neck or in the prostatic urethra Associated prostatic hyperplasia also could serve as an indication

Denervation of the bladder (section of pelvic nerves—nervi erigentes) As yet denervation of the bladder is not a standardized surgical procedure (Leadbetter and Shaffer), so that evaluation is not yet possible If it can be accurately executed, the operation should relieve spasticity of the detrusor musculature and of the smooth-muscle components of the vesical neck and prostatic urethra

Bilateral section of pudendal nerves This procedure was developed by Bors Cosbie Ross and his group in Liverpool now have by far the greatest experience with it It can be used for either complete or incomplete lesions because the resultant paralysis of the perineal muscles and anal sphincter is not too troublesome to the patient Bilateral sectioning of the pudendal nerves can be expected to produce 1) *certain* relaxation of the spastic external urethral sphincter, 2) *possible* relaxation of the vesical neck and prostatic urethra of varying degrees, depending on the proportion of striated muscle fibers present in these structures, and 3) *possible* reduction in spasticity of the detrusor musculature if reflex activity from spastic muscles of the perineum is a contributing factor in stimulating an irritable sacral portion of the spinal cord

Meirowsky's differential sacral neurotomy Theoretically, this is an interesting approach because it can be considered as a sort of "titration procedure," enabling the surgeon to cut just the right proportion of sacral root fibers (carrying both somatic and parasympathetic fibers) to restore normal "balance" to the bladder and its sphincters (For example, it is possible to cut the fibers of only the third sacral nerve roots or various combinations, such as the third and fourth sacral nerve roots and so on) This procedure can be used when complete lesions are present and also when incomplete lesions are at hand, if caution is used to avoid excessive weakening of the muscles of the buttocks, thighs, legs and feet which are partially innervated by sacral nerve roots The segmental distribution of motor fibers of the lumbar and sacral nerves is shown in figure 1 It must be realized, however, that this distribution varies greatly in individual cases Generally speaking, the fibers of the third, fourth and fifth sacral nerve roots usually can be cut without serious disability If the second sacral nerve roots are cut, detectable weakness will ensue If the first sacral nerve roots are cut, considerable weakness will follow The safest procedure, however, is to estimate this

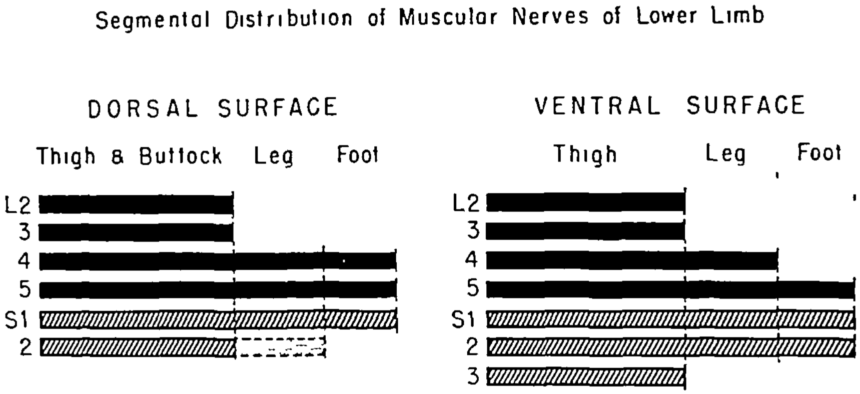

FIG 1 Segmental distribution of motor fibers of lumbar and sacral nerves

weakness before sectioning, by means of anesthetic blocks of the roots being considered for sectioning

What can differential sacral root neurotomy be expected to accomplish? It should be possible to obtain varying degrees of relaxation of the external urethral sphincter, vesical neck, prostatic urethra and detrusor musculature from relaxation of both striated and smooth muscle fibers, as explained above

Transurethral resection Transurethral resection should be able to relax both the vesical neck and prostatic urethra by removing both smooth and striated muscle fibers making up these structures, as well as any organic hypertrophy, fibrosis, or prostatic hyperplasia present This procedure is especially important against long-standing lesions which have caused muscular hypertrophy and fibrosis The operation also is especially applicable in the presence of nontraumatic neurologic lesions in men in middle and late life when varying degrees of prostatic hyperplasia are present

PREDICTING RESULTS OF NERVE SECTIONS, SUBARACHNOID INJECTION OF ALCOHOL AND THE LIKE

Fortunately, it is possible to predict with reasonable accuracy the results of nerve sections, alcohol block, selective cordectomy and so on, by prior simulation of the procedure by means of anesthetic blocks For instance, the subarachnoid injection of alcohol or selective cordectomy can be simulated by spinal anesthesia, section of the pudendal nerves by pudendal anesthetic block and differential sacral neurotomy by differential transsacral block Unfortunately, there is no diagnostic procedure to predict the results of transurethral resection

The results of diagnostic nerve blocks are evaluated in the following manner First, a urethrogram (either retrograde or one made at voiding) is made both before and after the block (while the anesthesia is still in effect) The degree of tonicity of the external sphincter is easily demonstrated (fig 2) The degree of spasticity and relaxation of the prostatic urethra and vesical neck is more difficult to evaluate (Damanski and Kerr)

Second, the patient's ability to void both before and after block is noted by

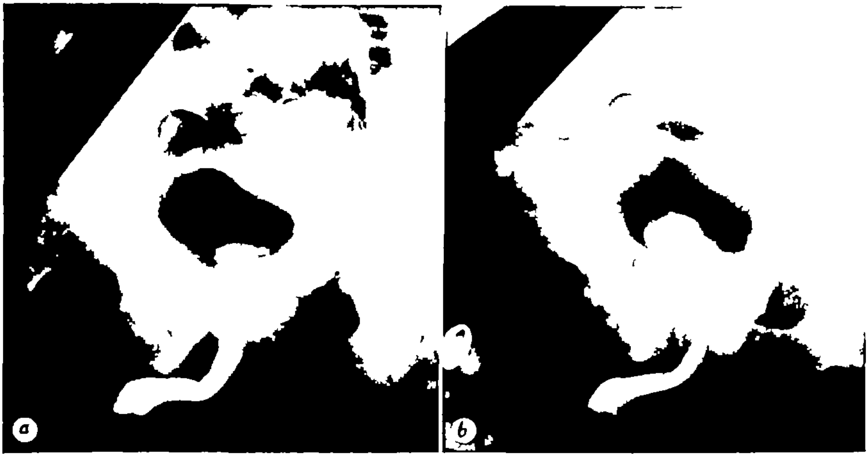

FIG 2 Urethrogram indicating spasticity A, before block B, after block (Reproduced, with permission of the publishers, from Emmett, J L, Daut, R V and Dunn, J H Role of the external urethral sphincter in the normal bladder and cord bladder J Urol, 59 439–454, 1948)

filling the bladder with fluid and requesting the patient to void by means of abdominal straining or manual Credé expression or both His ability to stop urination and the presence or absence of leakage while at rest are noted

Third, and finally, the vesical capacity and the amount of residual urine before and after blocking are determined

Other observations which also may be helpful, although they are more of academic interest, include cystometrograms and sphincter metrograms made before and after the anesthetic block

HOW TO CHOOSE THERAPEUTIC PROCEDURES

When therapeutic procedures are to be chosen in a given case, certain general principles must be kept in mind First, it should be remembered that nerve sectionings are destructive as well as final procedures that cannot be reversed The nerves cannot be joined together again On the other hand, transurethral resection is not a destructive procedure, no harm is done, no bridges have been burned, so to speak, and no complicating factor has been introduced, even if the procedure proves to be ineffectual

In the case of *complete permanent lesions,* no harm is done by nerve sectioning, alcohol block, cordectomy and so on, hence these procedures can be used more or less without hesitation, if diagnostic studies carried out with preliminary blocks suggest they will give good results In *incomplete lesions* the situation is much different, so that the various nerve blocks must be carefully considered to avoid results which might make the patient's general condition worse, increasing his disability and need for nursing care Generally speaking, when incomplete lesions are present, or when so-called medical lesions of the cord are at hand (and especially if the patient is a man past 40 years of age), my feeling is that transurethral resection should be tried first, and repeated if necessary If it fails, then the various types of sectioning should be considered

RESULTS OF SURGICAL PROCEDURES

A question frequently asked is, What results can be expected from these various procedures? It is difficult to answer this question with any degree of accuracy, but the following data may be helpful in forming some general conclusions

Sectioning of pudendal nerves Bors and Comarr (1954) wrote that they had used operations on the pudendal nerves (either neurotripsy or sectioning) for approximately 3 per cent, and transurethral resection for approximately 20 per cent, of 844 paraplegic persons Twenty-nine patients had undergone pudendal-nerve operations (either neurotripsy or sectioning) Of the 29, 11 had been treated by pudendal-nerve operation only, and 18 had undergone a combination of pudendal-nerve operation and transurethral resection Approximately three fourths of each group had regained "balanced function of the bladder "

Cosbie Ross (1956) reported the results of 29 bilateral pudendal-nerve sectioning (Mr Gibbon tells me that they have now done almost double that number) For 27 of the patients the sectionings were successful, as proved by Bors' criteria of relaxed anal sphincter and absent bulbocavernosus and anal reflexes Of these 27 patients, 19 (70 per cent) achieved good results, as evidenced by a dramatic reduction in the amount of residual urine Among the 8 patients for whom the operation was a failure, ultimate success was achieved for six by means of transurethral resection (three) and subarachnoid injection of alcohol (three)

Differential sacral neurotomy Meirowsky tested 115 paraplegic patients and found 18 suitable for this procedure Among the 18 he obtained good results for 13 (approximately three fourths)

Transurethral resection Results obtained from transurethral resection vary greatly in different hands, apparently because of the great variations in the completeness of the operation Some workers remove only a few pieces of tissue from the posterior vesical lip At the Mayo Clinic it has always been our policy to resect the entire circumference of the vesical neck We have found that it is not a simple procedure to neutralize completely the muscular activity of the vesical neck (and the prostatic urethra in the male) It often requires multiple operations and the removal of comparatively large amounts of tissue to accomplish this objective Our previous statistics (Emmett, Albers, and Anderson, 1951) are hardly applicable here, because the cases were not divided into those of upper motor neuron lesions and lower motor neuron lesions on the basis of Bors' criteria (relaxed anal sphincter and absent bulbocavernosus and anal reflexes) For the group as a whole, we felt we were able to expect good results in approximately one of three complete lesions and two of three incomplete lesions We observed that the patients who had "low lesions" in which abdominal muscles were intact, and the bladder appeared to be of the nonreflex (antonomous) type, could expect by far the best results from transurethral resection

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MANAGEMENT OF UROLOGICAL COMPLICATIONS IN 1000 PARAPLEGICS

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A great number of surgical procedures are necessary in the care of the complications which are a direct or indirect result of paraplegia

This study of the incidence and surgical management of genitourinary tract complications in 1000 paraplegics who have been under our care for the past 11 years was made primarily to determine whether or not our methods of treatment have resulted in a decrease in the number and severity of these complications The number and type of surgical procedures used in the treatment of these complications are tabulated as follows

SURGERY FOR UPPER URINARY TRACT COMPLICATIONS

Renal and ureteral calculi Although the surgical principles for the management of upper urinary tract calculi are the same in the paraplegic as the non-paraplegic, several points should be emphasized in applying these principles in the paralyzed patient Since symptoms are rarely present one must depend upon the routine use of excretory urography in the paraplegic who has an elevation of temperature of undetermined origin Surgery for the removal of renal or ureteral calculi not causing obstruction should be postponed until the patient is no longer confined to his bed

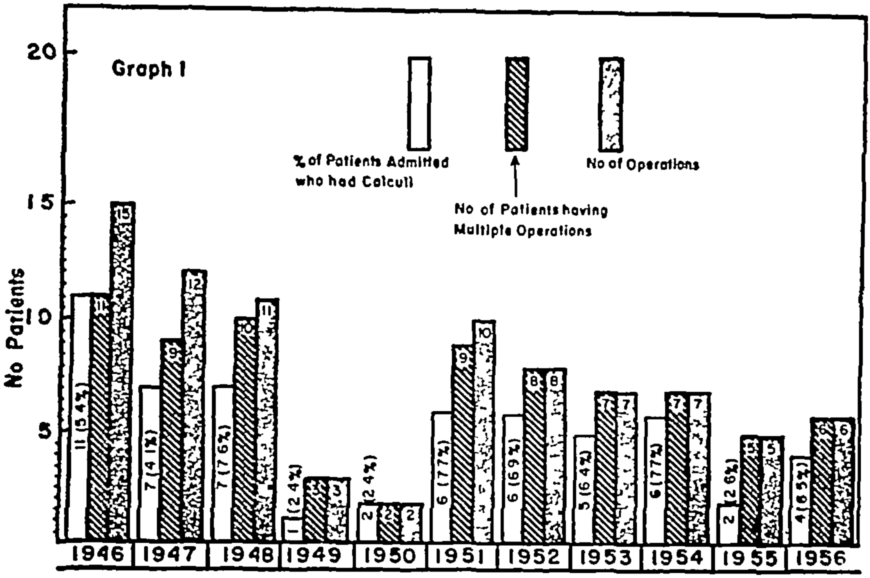
There is a definite increase in incidence of calculi in those patients with low cervical or high thoracic lesions where ambulation is delayed Hypercalcemia, present to some degree in the first few months in all paraplegics, also plays a part in the production of calculi but is probably only incidental, and without the presence of stasis and infection would not be of major importance Infection may be combated by forcing fluids and intermittent chemotherapy and antibiotics Early ambulation should be accomplished as soon as possible

Comment It will be noted in the graph (fig 1) that 57 patients, 5 7 per cent, among 1000 paraplegics acquired renal or ureteral calculi Forty-two were renal and 15 ureteral calculi Nine were bilateral and 48 unilateral

As shown by the graph, 20 patients required multiple procedures Two patients had four procedures, three, 3, and fifteen, 2 operations for removal of calculi We believe that only two patients had true recurrences and in nine "recurrence" was the result of the incomplete removal of calculi at the time of the previous operation In the remaining nine patients the calculi were bilateral, present either in the opposite kidney or ureter

Admittedly, these were a large number of repeat operations for the removal of calculi We believe it is of utmost importance to conserve renal tissue Only 1

Read at annual meeting of American Association of Genito-Urinary Surgeons, Hot Springs, Va., May 1-3, 1957



Surgical Procedure for Upper Urinary Tract Calculi

FIG 1

patient of this series required nephrectomy Three of the 57 patients have died in the past 11 years Two are listed as dying from calculous pyonephrosis One died with adrenal insufficiency the second day following surgery

It will be noted that for the first 3 years following World War II, a large number of patients had calculi that required surgery The rate declined until 1951 at which time we began receiving the Korean War veterans Again there was slight increase in the incidence which has slowly decreased and has remained stable for the past 4 years

Two important findings may be noted First, most of the stones form within the first 12–36 months following cord injury, and secondly, although not shown on the graph, the incidence of calculi in our series has been in direct proportion to the number of new cases admitted, varying from 2 5 per cent of 40 patients admitted in 1949 to 7 8 per cent of 79 patients admitted in 1951 Of 612 patients who entered the hospital prior to 1951, 4 7 per cent acquired calculi and 6 7 per cent of 488 have been treated for calculi subsequent to the onset of the Korean War These figures vary widely from those where the total number of patients occupying beds at any given time is the basis for the compilation

We were somewhat surprised with our findings of a rather stable percentage ratio of patients who developed calculi over the past 11 years But when our methods for prevention of calculi were analyzed it was noted that our methods had changed very little, if at all Also, the great majority were admitted to our hospital several months following injury

Nephrostomy drainage Nephrostomy drainage, to preserve the failing function of damaged kidneys or as a means of drainage following nephrolithotomy, was performed 36 times on 27 patients Twenty had operations for pyelectasis resulting from vesicoureteral reflux, one for obstruction following vesicoureteral

TABLE 1 *Incidence of nephrostomy drainage*

	Year											Total
	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956	
No patients	0	7	6	2	4	3	2	0	2	1	0	27
No operations	0	9	9	3	5	5	2	0	2	1	0	36

plasty, one for destruction of the upper ureter by gunshot, and five for pyelectasis due to calculi Seven of these patients are now dead from renal insufficiency Of these, four had vesicoureteral reflux, two had reflux plus calculi and one, calculi alone

Comment It will be noted from table 1 that 19 patients required 26 nephrostomies before 1950 The majority of these were carried out for pyelectasis due to vesicoureteral reflux Since 1950, at which time we began treating vesicoureteral reflux by plastic repair of the vesicoureteral junction, only eight patients have required nephrostomy Two of these were carried out preliminary to plastic repair of the vesicoureteral junction and one to afford drainage for obstruction of the ureter subsequent to vesicoureteral plasty The remaining five patients had nephrostomy drainage following removal of calculi

Complications requiring nephrectomy As stated before, the conservation of renal tissue in the paraplegic is of prime importance Nephrectomy has only been necessary in five of the 1000 patients, all were for pyohydronephrosis Calculi were present in two of the five patients

Complications requiring skin ureterostomy Only two patients have had a total of three skin ureterostomies One patient with severe spinal arthritis required bilateral skin ureterostomy following recurrence of renal calculi The second patient with a single kidney required skin ureterostomy for a megaloureter and pyelectasis due to reflux

Complications requiring vesicoureteral plasty Since April 1946, 136 (13 6 per cent) of the 1000 patients who have been admitted to our Paraplegic Service have had reflux of clinical significance In 1950 we began to concentrate our attack directly on the vesicoureteral junction for the treatment of vesicoureteral reflux It is our opinion that reflux in these patients is the result of anatomical changes in or near the vesicoureteral opening These changes are indirectly associated with cord injury and probably result from erratic impulses originating in the distal stump of the cord, causing the bladder to become trabeculated and contracted The complications that accompany cord injury such as bladder stones, prolonged cystitis and the ever present foreign body (catheter or suprapubic tube) are probably also factors in the development of reflux in the paraplegic

After several unsuccessful attempts to alleviate reflux by simple reimplantation of the ureter, an operative procedure was devised at our hospital which has three principles First, the attachment of the ureter to the trigone is preserved, second, a long intravesical ureter is constructed, and third, the bladder wall behind the ureter is reinforced

TABLE 2 *Incidence and results of vesicoureteral plasty*

Year	Patients	Ureters	Success	Failure	Obstruction	Reflux
1950	5	6	5	1	0	1
1951	8	14	11	3	0	3
1952	3	5	5	0	0	0
1953	3	5	2	3	1	2
1954	3	5	4	1	0	1
1955	6	11	8	3	2	1
1956	3	5	3	2	2	0
Total	31	51	38	13	5	8

To date this procedure has been performed in those patients in whom the reflux did not disappear under routine catheter drainage (20 per cent in our patients) These patients for the most part had a mild reflux without evidence of irreversible anatomical changes in or near the ureteral orifice Our indications and criteria for surgical correction of reflux are 1) X-ray evidence of damage to the upper urinary tract 2) In the absence of upper urinary tract damage, as depicted by x-ray, repeated attacks of pyelonephritis serve as an indication 3) The reflux should be permanent and irreversible as shown by cystoscopic inspection and repeated cystograms at monthly intervals of at least three months

Comment Since 1950, vesicoureteral plasty has been carried out on 31 patients and 51 ureters (table 2) Thirty-eight of these were successful, our criteria for a good result being first, no reflux present, second, same or improved pyelograms, and third, clinical improvement Thirteen procedures were failures, eight being due to recurrence of reflux and five to obstruction at the site of operation The early recurrences of reflux and postoperative obstruction are due to faulty surgical technique Late recurring reflux results from failure to eliminate the etiologic basis for the reflux One death occurred in this series five days following operation due to a fulminating pyelonephritis

It will be noted in table 2 that a fairly even number of patients throughout the past 7 years have required vesicoureteral plasty for reflux We cannot expect a marked decrease in the number of paraplegic patients who acquire reflux inasmuch as a definite percentage who have spastic hypertonic bladders will acquire anatomical changes near the ureterovesical junction that will produce reflux

Suprapubic cystostomy Cystostomy is indicated whenever drainage of the bladder by urethral catheter is impractical Lack of facilities for close observation and nursing care is the most common reason for its use Other indications are incontinence in the female, periurethritis, periurethral abscesses and recurrent epididymitis

TABLE 3 *Incidence of cystostomy drainage*

	Year											Total
	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956	
No operations	1	0	2	3	4	7	3	2	1	3	1	27

Comment The majority of the cystostomies shown in table 3 were carried out on those quadriplegics in whom a satisfactory reflex bladder failed to develop Several had cystostomy drainage preliminary to repair of urethral fistula and diverticulum Four required cystostomy for removal of large bladder calculi It is apparent from table 3 that cystostomy drainage as a means of diversion has not been used by us routinely It is our opinion that the bladder is not allowed to act as a single physiologic functioning unit when there is a break in the continuity of the bladder musculature produced by cystostomy Rehabilitation is prolonged, as extra time is required for healing of the suprapubic fistula In most patients who have prolonged cystostomy drainage it is necessary to increase the capacity of the bladder following discontinuance of drainage

In a survey made by us in which we compared the end results of bladder function following urethral or cystostomy drainage, we noted that poorly functioning bladders were found more often and vesicoureteral reflux was present in a higher percentage of the patients who had drainage by cystostomy The most serious complication resulting from cystostomy drainage is discussed below

Surgical closure of suprapubic fistula Cystostomy wounds fail to close in some patients primarily because they have been improperly performed, the tract having been established too close to the symphysis pubis Other factors that may be present are the development of a fibrotic epithelized tract, the presence of infection at all times, and a "neurogenic factor" coupled with a diminution in tonicity of the abdominal musculature The seriousness of this complication was manifested to us when the postmortem examination in three deaths on our service showed that only the distal portion of the sinus had healed and the unhealed fibrotic barrier of the unobliterated juxtavesical portion was overcome This resulted in fatal peritonitis by direct contiguity in two patients, and by direct rupture into the peritoneal cavity in the third

Comment It will be noted in table 4 that the majority of cystostomy closures were necessary immediately following World War II followed by a decline in number until 1951 near the end of the Korean War Not until the latter months of World War II, when transportation of all casualties by air was accomplished, was it possible to use urethral drainage Also, the general surgical personnel probably had not been instructed as to the correct method of performing cystostomy This resulted in many suprapubic tubes being brought out just above the symphysis pubis Our findings since 1952 show that either cystostomy as a means of drainage has been abandoned by many, or when resorted to, has been properly performed

Transurethral resection of the bladder neck Resection of the hypertrophied or spastic bladder neck is undoubtedly the best single means of converting an unbalanced to a balanced neurogenic bladder It is well recognized that there is a

TABLE 4 *Incidence of closure of suprapubic fistula*

	Year											Total
	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956	
No operations	25	9	8	7	5	10	0	0	0	3	0	67

TABLE 2 *Incidence and results of vesicoureteral plasty*

Year	Patients	Ureters	Success	Failure	Obstruction	Reflux
1950	5	6	5	1	0	1
1951	8	14	11	3	0	3
1952	3	5	5	0	0	0
1953	3	5	2	3	1	2
1954	3	5	4	1	0	1
1955	6	11	8	3	2	1
1956	3	5	3	2	2	0
Total	31	51	38	13	5	8

To date this procedure has been performed in those patients in whom the reflux did not disappear under routine catheter drainage (20 per cent in our patients) These patients for the most part had a mild reflux without evidence of irreversible anatomical changes in or near the ureteral orifice Our indications and criteria for surgical correction of reflux are 1) X-ray evidence of damage to the upper urinary tract 2) In the absence of upper urinary tract damage, as depicted by x-ray, repeated attacks of pyelonephritis serve as an indication 3) The reflux should be permanent and irreversible as shown by cystoscopic inspection and repeated cystograms at monthly intervals of at least three months

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TABLE 3 *Incidence of cystostomy drainage*

	Year											Total
	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956	
No operations	1	0	2	3	4	7	3	2	1	3	1	27

TABLE 7 *Number of fistulas and diverticula repaired*

	Year											Total
	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956	
No fistulas	14	11	15	15	12	12	10	4	3	7	3	106
No diverticula	1	0	5	10	3	5	11	2	2	3	3	46

TABLE 8 *Number of procedures required to repair fistulas in 67 patients and diverticula in 41 patients*

Fistulas

No of Fistulas Repaired	Total No. of Patients	Percentage of Patients	Total No of Fistulas Repaired
1	45	67	45
2	12	18	24
3	6	9	18
4	2	3	8
5	1	1 5	5
6	1	1 5	6
Total	67	100%	106

Diverticula

No. of Diverticula Repaired	Total No of Patients	Percentage of Patients	Total No of Diverticula Repaired
1	36	88	36
2	5	12	10
Total	41	100%	46

SURGERY FOR LOWER URINARY TRACT COMPLICATIONS

Urethral fistula and diverticulum These two complications are considered together since each is a sequela to periurethral infection

Comment There are several interesting findings found in tables 7 and 8 Many fistulas and diverticula occurred following attempts to place these patients on urethral catheter drainage There has been a decline in the number requiring surgery in the past 4 years This, we believe, may be attributed to the use of small catheters and the prevention of an acute angulation of the urethra at the penoscrotal junction by taping the penis back on the lower abdomen This reduction in the number of operative procedures is not a true index of the number of patients who acquire urethral fistulas as a much larger percentage at the present do not require surgical closure The use of clorpactin irrigations per urethram and fistula has resulted in the prompt healing of many fistulas in the past two years Surgery is still necessary for elimination of the well-formed diverticulum

We are all aware of the surgical difficulties encountered in the abolition of the

TABLE 5 *Number of transurethral resections of bladder neck*

	Year											Total
	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956	
No operations	8	5	30	22	26	28	24	28	27	21	19	239

TABLE 6 *Number of transurethral resections on 188 patients*

No Tur's	No Patients	% Patients	Total No Tur's
1	150	63 1	150
2	26	21 8	53
3	11	13 8	33
4	1	1 3	4
Totals	188	100%	239

balance of power existing between opposite forces, namely the detrusor for expelling the urine and the obstructive sphincteric mechanism of the internal orifice and, rarely, the external urethral sphincter Although there is a difference of opinion as to the presence of a true mechanical obstruction, there can be little doubt that a high percentage of patients are benefited by resection whether it be due to the removal of true hypertrophied tissue or elimination of spasm of the internal orifice

Comment From tables 5 and 6 we note that 188 or 18 8 per cent of 1000 paraplegics had transurethral resection Thirty-eight patients required multiple procedures This is a smaller number of multiple procedures than reported by others We are of the opinion that the resection should include the entire circumference of the bladder neck with resection of all tissue back to the verumontanum, as removal of the bladder neck alone may result in obstruction from a minimal amount of tissue near the veru which is made prominent by resection of the bladder neck

We believe that transurethral resection should be postponed if possible until all conservative methods for bringing the bladder into balance have been attempted During the years 1946 and 1947 only 13 patients had resections If possible we wait at least one year before resorting to resection Eighty-five per cent of our patients had good or fair results There were no postoperative deaths Bleeding was rarely troublesome There has been very little yearly change in the number of resections considered necessary over the past nine years (1948–1956)

Surgery for bladder calculi Bladder calculi are of frequent occurrence in the paraplegic It is our estimate that at least 50 per cent of our patients have at one time had calculi, usually of the "eggshell" variety It has been necessary in only four instances to remove these calculi by a suprapubic procedure The eggshell type is readily removed by the Ellik evacuator or the Lowsley grasping forceps During the past year we have placed a group of patients on salicylamide and these patients have rarely acquired bladder calculi been used much less frequently by others in the past five years Also, it has been noted that cystostomy is now correctly performed in the great majority of paraplegic patients entering our hospital

The number of patients who acquire reflux of clinical significance is 13 6 per cent In our series 22 per cent have been irreversible and required vesicoureteral plasty This incidence of reflux has remained stable over the past eight years and cannot be expected to change until we are able to eliminate the factors that cause reflux

Transurethral resection of the bladder neck has been performed on 188, 18 8 per cent, of our patients This yearly ratio has varied only slightly over the past 9 years

There has been a decrease in the number of patients who acquire urethral fistulas and diverticula and a greater decrease in the number who require surgical correction

The paraplegic patient withstands urological surgical procedures unusually well There were two postoperative deaths following 723 operative procedures

TABLE 9 *Yearly number of perineal urethrostomies and repair of perineal fistula*

	Year											Total
	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956	
Perineal urethrostomy	0	11	14	8	3	11	9	10	9	14	10	101
Repair of perineal urethral fistula	1	0	6	10	7	8	0	4	7	4	0	47

fistulous tract in the urethra As shown by table 8, only 45 fistulas were eliminated by one procedure Twenty-two required a total of 61 procedures before the fistulas were finally cured Diversion of the urinary stream is necessary in most patients before definitive surgery on a fistula or diverticulum is attempted

Perineal urethrostomy and repair of perineal urethrostomy Perineal urethrostomy was most often performed for urinary diversion preliminary to repair of diverticulum or fistula Only on the rare occasion was it used for drainage

Comment The number of diversionary urethral procedures has remained fairly steady over the past 10 years Here again we note the poor healing that occurs in the paraplegic's urethra Forty-seven procedures were required to close perineal urethrostomy fistulas in 37 patients

Epididymectomy and/or orchiectomy As vasectomy was never carried out in these patients (this being the patients' desire), 20 per cent of the 1000 patients acquired genital infection Twenty-eight or 2 8 per cent required epididymectomy and/or orchiectomy This might appear as a rather high percentage However, if one considers the more rapid rehabilitation with less damage to the bladder and upper urinary tract, this percentage is not prohibitive Also in a study of the testicles removed at postmortem examination on 27 paraplegics, many with liver disease (failure to detoxify or metabolize the estrogens), it was found that 24 had from grade 1 to 3 atrophy of the testicles

SUMMARY AND CONCLUSIONS

Many urological surgical procedures are necessary to treat the complications resulting from cord injury or disease and those complications that arise during rehabilitation of these patients Six hundred twenty-three of 1000 patients had 723 urological operative procedures These statistics do not include 500-plus cystoscopic removal of bladder calculi and 50-plus neurosurgical procedures used in the urological care of these 1000 patients

The incidence of operative procedures for removal of calculi of the upper urinary tract in 1000 patients was 5 7 per cent Surprisingly, this ratio has remained at an even rate over the past 11 years

Nephrostomy drainage has been rarely necessary in the past five years Repeated examinations and continuous observation have resulted in the early detection and correction of factors that might lead to renal destruction thus obviating the necessity of nephrostomy drainage

Cystostomy as a means of drainage has never been practiced by us and has urethra (Kollmann's dilator was used in some of these patients, with only momentary effect.)

In view of the generally poor prognosis in paraplegics without efficient bladder function (Damanski and Gibbon, 1956), we thought it justifiable to attempt to relieve the retention by resection of the external sphincter. As only two of our patients had retained spinal reflex detrusor contractions, the expulsive forces in the majority were poor, especially among the quadriplegics, and it seemed that, for successful results, the urethral resistance would have to be reduced to a minimum. We had no way of estimating the location and extent of the resection which would be required to achieve this object, and our technique was at first dictated mainly by considerations of convenience and safety. Up to date, we have thought it unwise to introduce modifications, but further experience may change our attitude.

THE OPERATION

We employ the cold punch, resecting three to five strips posterolaterally at the level of the external sphincter. This exposes open tissue spaces, and sets up considerable hemorrhage, mainly venous. Electrocoagulation is ineffectual, and we rely on the immediate insertion of a large three-way Foley catheter (F22 to 26) using a curved introducer if any resistance is met at the site of resection. Blood transfusions and an appropriate antibiotic are given routinely. In a few cases, the opportunity has been taken to resect the bladder neck also, despite its wide open appearance. If this procedure seems indicated, it should be done first, as it is unwise to prolong the operation once the external sphincter has been dealt with, on account of the risk of perineal extravasation. This occurred in one of our early cases, and at the end of the operation the scrotum was found to be greatly distended with fluid. As isotonic glycine was being used, and as the urine was relatively uninfected, reliance was placed upon simple elevation of the scrotum. Fortunately, the condition settled down rapidly without complications.

Continuous irrigation is usually employed postoperatively, and the larger catheter is replaced by a smaller one within twenty-four hours or so.

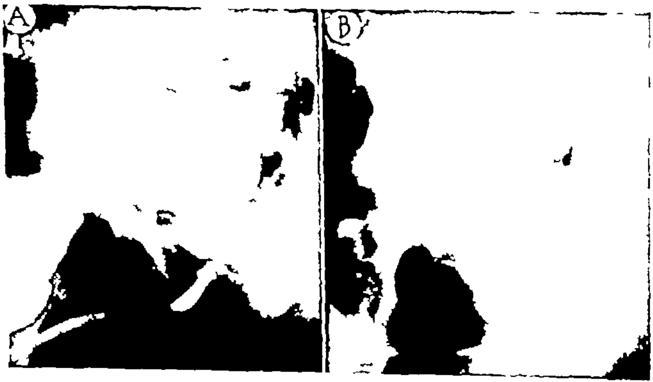

Fig. 1. Case 10. N. C. Oblique cystourethrograms. A, February 6, 1957, preoperatively. B, March 6, postoperatively.

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RESECTION OF THE EXTERNAL URETHRAL SPHINCTER IN THE PARAPLEGIC—PRELIMINARY REPORT

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All those concerned with the treatment of paraplegia will be familiar with that hard core of cases in which retention of urine persists despite all attempts to reduce the resistance of the urethral canal In some of these cases, the obstruction can be localized to the level of the external sphincter, and we propose to confine our attention to this group It should be emphasised at this point that we are not referring to cases with spasticity in this region, as it has been shown in recent years that the spastic external sphincter can be dealt with by denervation, whether by subarachnoid alcohol injection or by pudendal neurectomy It is noteworthy, however, that this denervation does not usually produce more than a mild form of stress incontinence, even when the internal sphincter has been resected Leakage of urine is presumably prevented by the elastic pressure of the periurethral tissues If this pressure is excessive, or if it is accompanied by angulation of the urethra, complete obstruction may result, as noted by Watkins (1936)

There is no true stricture in these cases, and even forcible dilatation is followed by only a brief period of improvement For this reason, Donovan (1947) suggested punching out the region of the membranous urethra He anticipated total incontinence as the price which would have to be paid for relief of the retention, and it is probable that this danger has deterred many urologists from attempting the operation It has been performed successfully, however, at least once outside our own unit (Bors and Comarr personal communication), and our experience, now to be related, provides further evidence of the value of the procedure, and suggests that the risk of incontinence has been exaggerated

We have now resected the external urethral sphincter for nonspastic obstruction thirteen times in ten patients, of whom all but one (a case of advanced disseminated sclerosis) had a complete cord lesion Four of the five quadriplegics had sustained a fracture-dislocation, and, of the paraplegics, the lesion was of traumatic origin in three All had the following features in common

1) Complete or almost complete retention of urine

2) Localization of the obstruction at the level of the external sphincter, radiologically and sometimes endoscopically (In four cases, bladder neck resection had already been performed)

3) Absence of spasticity in the external sphincter region, as judged by the state of the anal and bulbocavernosus reflexes (All the quadriplegics had had one or more subarachnoid alcohol blocks, and all the paraplegics had undergone pudendal neurectomy)

4) Easy instrumentation, except perhaps for angulation of the membranous

Read at annual meeting of American Association of Genito-Urinary Surgeons, Hot Springs, Va , May 1–3, 1957 urethra. (Kollmann's dilator was used in some of these patients, with only momentary effect.)

In view of the generally poor prognosis in paraplegics without efficient bladder function (Damanski and Gibbon, 1956), we thought it justifiable to attempt to relieve the retention by resection of the external sphincter. As only two of our patients had retained spinal reflex detrusor contractions, the expulsive forces in the majority were poor, especially among the quadriplegics, and it seemed that, for successful results, the urethral resistance would have to be reduced to a minimum. We had no way of estimating the location and extent of the resection which would be required to achieve this object, and our technique was at first dictated mainly by considerations of convenience and safety. Up to date, we have thought it unwise to introduce modifications, but further experience may change our attitude.

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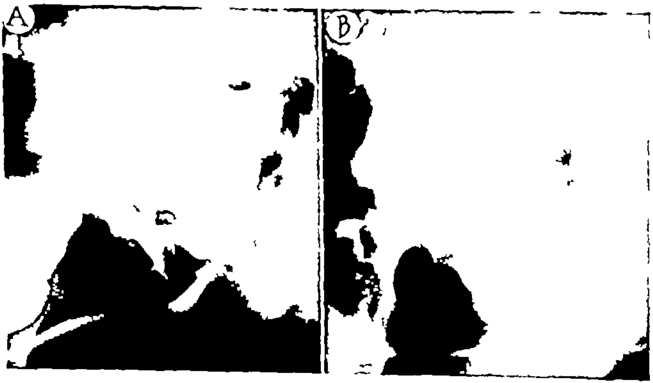

FIG. 1. Case 10. N. C. Oblique cystourethrograms. A, February 6, 1957, preoperatively. B, March 6, postoperatively.

COMPLICATIONS

There have been two deaths one patient who had gross urinary infection preoperatively succumbed to repeated secondary hemorrhage, while the other, who died from uremia, was known to have bilateral ureteral reflux with hydronephrosis and poor renal function

Apart from the fatal case, in three patients secondary hemorrhage developed, indicating the severity of their chronic urinary infection Only in one case did late extravasation occur, and it was countered successfully by perineal drainage and suprapubic cystostomy

RESULTS

The surviving eight cases have all been relieved of retention In three patients, the resection had to be repeated before a satisfactory result was obtained In one of these, perineal division of the external sphincter had been tried without success

1) *Residual urine* This was reduced to nil in five cases and to six to eight ounces in the others

2) *Cystourethrography* Radiological improvement in the caliber of the mem-

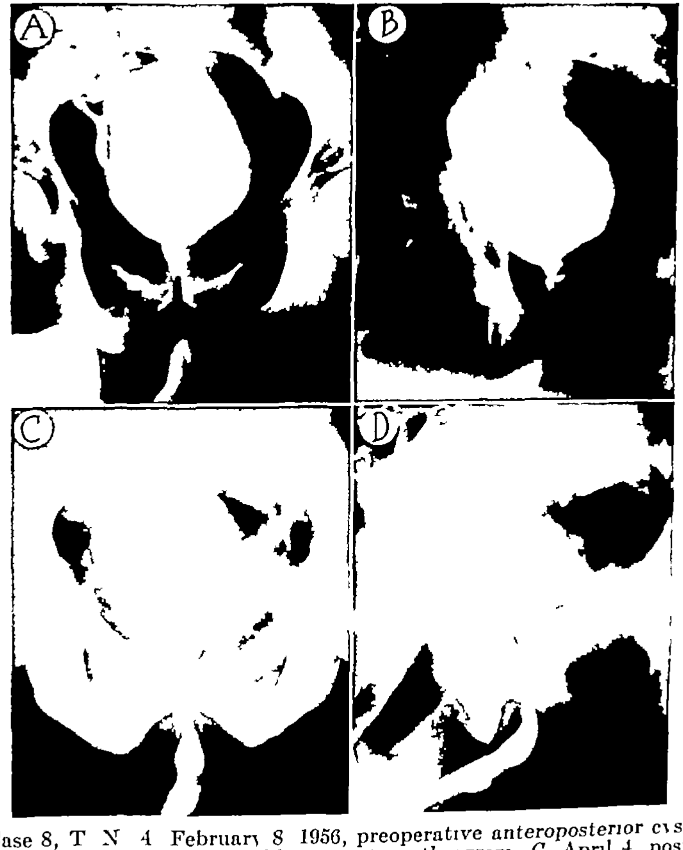

Fig 2 Case 8, T N A February 8 1956, preoperative anteroposterior cystourethrogram *B*, February 8 preoperative oblique cystourethrogram *C* April 4 postoperative anteroposterior cystourethrogram *D* April 4, postoperative oblique cystourethrogram

branous urethra was marked in four cases (figs 1 and 2) moderate in one and doubtful or absent in the remainder

3) *Ureteric reflux* Four cases had unilateral reflux preoperatively and in only two was this abolished In one case, backflow was first demonstrated after the resection

4) *Hydronephrosis* In two cases with pre-existing hydronephrosis the pyelograms had reverted to normal four and six months postoperatively there having been no vesical drainage in the interim (figs 3 and 4)

5) *Infection* In only one case did the urine become sterile, but in at least two others the infection diminished noticeably

The degree of stress incontinence which these patients experience is similar to that found in the average cauda equina lesion and they find it necessary to wear a urinal for special occasions and often at night as well In no case has there developed continuous dribbling from an empty bladder

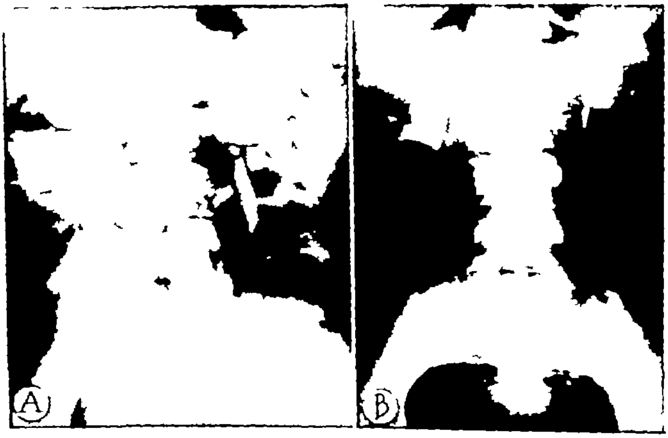

Fig 3 Case 1 J H Excretory pyelograms A February 22 1956 preoperatively B June 20 three months postoperatively

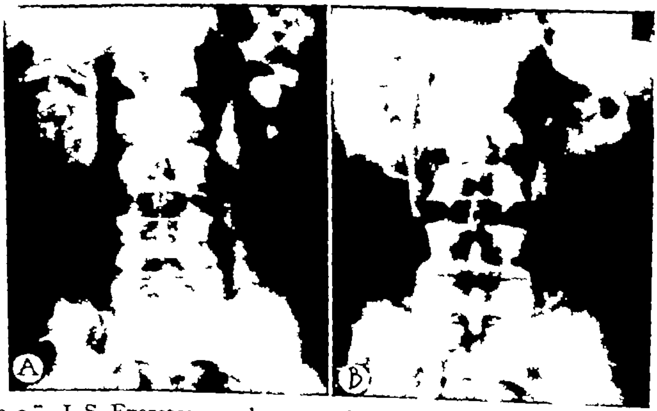

Fig 4 Case 7 J S Excretory pyelograms A July 18, 1956 preoperatively B, January 30 1957 4 months postoperatively

CONCLUSIONS

Resection of the nonspastic external urethral sphincter seems to be effective in relieving the obstruction without increasing to any serious degree the risk of incontinence It is probably a dangerous procedure (as, indeed, are other urological operations) in cases with severe infection resistant to antibiotics, and in those with bilateral hydronephrosis, especially in the presence of reflux In these unfavorable circumstances, it may be safer to persevere with a perineal approach However, in our more recent cases, we have been much more successful in preventing or clearing up preoperative infection, by employing the fine plastic catheters which we have been developing for several years (Ross, Damanski and Gibbon, 1957) We also revert to the use of these catheters as soon as possible after the operation, and we feel that they greatly diminish the risk of surgery in these difficult cases, by minimizing the inevitable urethritis

It is possible, moreover, that this operation may find a place in the treatment of the spastic external sphincter, as it does not produce the impotence which inevitably follows subarachnoid alcohol block or pudendal neurectomy Comarr (1957) has already reported two such cases treated successfully in this way The merits of transurethral resection for this purpose must, however, be compared with those of electrocoagulation of the sphincter (Baumrucker, 1948) and urethrolysis (Semans, 1950) The latter operation was conceived by its author as a form of peripheral denervation of the sphincter, but the incontinence produced seems more severe than would be expected on such basis Some modification might be worth a trial

Further reports of the effects of various procedures in the difficult type of case considered in this paper are urgently required to clarify the indications for resection of the external sphincter

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VESICOURETERAL REFLUX IN PARAPLEGIC PATIENTS

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The most formidable of all urinary tract complications in 1000 paraplegics treated by us since April 1946 has been vesicoureteral reflux. In 136 (13.6 per cent) reflux of clinical significance has developed.

ETIOLOGY

Considerable controversy exists as to the mechanism of the development of reflux in the paraplegic. It has been stated that the reflux which develops is the direct result of interruption of the ureteral nerve supply. We do not agree with this theory for the following reasons:

1) Failure of the majority of patients with corresponding neurological lesions to acquire reflux.

2) The unilateral incidence in some instances although the spinal transection is complete.

3) The occasional remission or improvement.

4) No normal nerve connections with the central nervous system have as yet been demonstrated, the interruption of which will cause reflux.

5) The excised bladder or the bladder in the cadaver may be filled to the point of rupture without reflux taking place.

Obstruction at or below the bladder neck is not a primary factor in the formation of reflux in these patients (although we have noted reflux with the same anatomical changes in or near the ureteral meatus in the patient with bladder neck obstruction). Practically all paraplegic patients have free, uninterrupted drainage either by suprapubic tube or urethral catheter.

It is our opinion that the reflux which develops in the cord injury patient is the result of anatomical changes in or near the vesicoureteral orifice. These changes are indirectly associated with cord injury and probably result from erratic nervous impulses originating in the distal stump of the spinal cord causing the bladder to become contracted and trabeculated. The complications that accompany cord injury such as bladder stones and prolonged cystitis are probably also a factor in the development of reflux. In support of our theory are the following:

Disappearance occasionally of the reflux when the caliber and degree of trabeculation of the bladder are lessened. This has been noted after the subsidence of very severe cystitis or removal of bladder calculi. In 20 per cent of our patients the reflux disappeared with catheter drainage. Secondly, the conversion of an upper motor neuron lesion to a lower motor neuron lesion by subarachnoid alcohol injection has resulted in the elimination of hydroureter and nephrosis and reflux. As first suggested by Graves and Davidoff and repeatedly stated by Em-

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mett and us, a prerequisite for the development of reflux in all but the rare case is that there be "a sustained tonus of the bladder as it actively resists filling," coupled with a diminished sensitivity of the bladder to fill and stimuli In 1952 in my discussion of a paper by Drs Brendler, Dean and others, in which they described their experiences with rhizotomy in the treatment of the advanced paraplegic bladder, they noted marked improvement in the dilated upper urinary tract in three of four patients At that time I reported the loss of reflux in 2 patients following subarachnoid alcohol injection Hutch in 1956 reported the loss of reflux in one patient and improvement in the degree of hydronephrosis and hydroureter in three others by elimination of the sacral reflex arc This slide* is that of a patient in whom mild reflux and hydroureter and nephrosis developed in his remaining right kidney, the 30-minute excretory urogram to your right was made 5 days following subarachnoid alcohol injection and shows much improvement

Within the past 2 months we have carried out subarachnoid alcohol injection in 2 patients and sacral rhizotomy in one patient (S_2, S_3, S_4) who had reflux and hydroureter and nephrosis All have improvement in the degree of dilatation of the upper urinary tract

This is an excretory urogram of a patient with nonobstructive hydronephrosis on the left, which showed marked improvement 9 days following subarachnoid alcohol injection

This is a pre- and a post subarachnoid injection cystogram in the same patient showing decrease in the degree of reflux We believe that this is further evidence that the same forces are at play in nonobstructive hydronephrosis with or without reflux

There is a possibility that the reflux may be completely eliminated in these two patients in time In the patients reported by Hutch, optimum improvement was found only after the elapse of 6 to 21 months Permanent reflux has not developed in any of our patients with a complete lower motor neuron lesion and atonic bladder

Further evidence in support of our hypothesis is x-ray evidence of a diverticulum or cellule in or near the ureteral meatus which results in loss of support behind the intramural ureter, there no longer being firm bladder musculature behind the ureter for it to be compressed against by inward intravesical pressure Study of 136 cystograms showing reflux revealed a small diverticulum or cellule to be present in the region of the vesicoureteral opening in 65 per cent

Cystoscopic examination confirmed the x-ray findings The small diverticulum was found to lie above and lateral to the ureteral orifice When a ureteral catheter is passed through the ureteral orifice, it will outline the ureter passing under the floor of the saccule All had trabeculation of the bladder

Another finding in those patients with a well developed saccule was displacement and loss of obliquity of the intramural ureter which retains its caliber although the ureter is dilated above the portion

A photomicrograph taken from the BULLETIN OF THE JOHNS HOPKINS HOSPITAL of 1903 depicts a sagittal section of the normal vesicoureteral junction and the distortion that results from the presence of a diverticulum in this region It is noted that the intramural ureter has assumed an extravesical position with a loss of its obliquity and muscular support beneath

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* Reproduction of slides will not be made

This schematic drawing of the vesicoureteral junction depicts what probably occurs when the vesical wall behind the intramural ureter is weakened Point X where the ureter normally enters the bladder is now found to lie a few millimeters to a centimeter beyond the outer bladder wall

Obstruction, either functional or mechanical, is probably always present with and almost always precedes reflux In observations made on our cystograms with and without reflux it was noted in a high percentage of the x-rays that there was a sudden interruption of the contrast material in the ureter a few millimeters to a centimeter before it entered the bladder wall This area had all the appearances of a strictured area but it has been found that large caliber ureteral catheters and bulbs will pass this point with ease

The intramural ureter has no circular fibers and is unable to propel the urine through the bladder wall and acts only as a conduit and then only if it is supported by Waldeyer's sheath and a firm bladder wall behind it When sacculation occurs the intramural ureter becomes extravesical losing its normal support Having no propulsive force of its own and with a loss of support, the intramural ureter now acts as an obstruction It is known that the intramural and intravesical ureter has no circular fibers and that dilatation of the ureter must involve weakening of the circular fibers as noted in the ureter above the bladder

The hydronephrosis and hydroureter found in reflux may also result from a mechanical obstruction due to acute angulation of the displaced extravesical ureter

TREATMENT

After several unsuccessful attempts to alleviate reflux by simple reimplantation of the ureter, an operative procedure was devised at our hospital which has three principles First, the attachment of the ureter to the trigone is preserved, second, a long intravesical ureter is constructed, and third, the bladder wall behind the ureter is reinforced

Thirty-one cord injury patients have had repairs of vesicoureteral reflux In 11 the reflux was unilateral and in 20 bilateral In 38 ureters the procedure was successful and 13 were failures

We have found that the recurrence of reflux in our patients has happened immediately (5 ureters) following repair or several months afterwards (3 ureters) On cystoscopic inspection of the patient in whom recurrence is immediate, it is noted that the ureter has retracted to its original bed We believe this may be due to faulty technique at the time of the operative procedure and may result from incomplete mobilization of the lower one-third of the ureter The ureter should be dissected free so that it may adjust to its new course through the bladder wall without tension and will not retract to its former position

In those patients who have a delayed recurrence, we feel that there has been a failure to eliminate the factors which caused the reflux

Obstruction, by far the more serious complication, may be partial and temporary as seen in three ureters of our series We attribute temporary obstruction to postoperative edema or tight suturing around the ureter at its exit from the bladder Permanent ureteral obstruction may vary from a slight increase in dilatation of the lower ureter to complete obstruction In analyzing our patients who have acquired permanent obstruction, we believe that the ureter was not allowed to pass through the bladder wall loosely and without tension or angulation over the area from which it was dissected Acute angulation results from tight suturing beneath the intravesical ureter near its exit combined with improper fixation sutures

In one of our patients, an intraureteric fibrous band formed between the newly created intravesical ureters producing an acute medial angulation Resection of this band resulted in the immediate retraction of the nipples to a lateral position, thus relieving the obstruction

COMMENT

Vesicoureteral reflux in the paraplegic is the result of anatomical changes in or near the intramural ureter produced by factors which cause a sustained hypertonicity of the bladder In the paraplegic, this hypertonicity is probably due to the continuous bombardment of the bladder by impulses originating from the isolated sacral reflex centers

Possibly in the future, if we are able to determine the precise pathogenesis and are successful in eliminating the cause of reflux in the paraplegic in its incipiency, by denervation of the bladder, vesicoureteral plasty will then only be necessary in the patient who acquires irreversible reflux

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SURGICAL PROCEDURES ON THE VESICAL NECK

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No clinical urologic condition requires more deliberate consideration in the planning of its management than vesical dysfunction due to spina bifida One is attempting to convert a lesion that is physically disabling and socially incompatible into one that will permit a reasonable degree of physical well being and allow the individual to live in a fairly normal environment

The objectives in the treatment of vesical dysfunction due to spina bifida are to restore urinary control, eliminate residual urine, preserve renal function and eliminate infection of the urinary tract In trying to achieve these objectives one attempts to substitute mechanical procedures for a normal nerve supply that will enable the lower urinary tract to perform some semblance of normal function

It should be recognized that an ideal result will not be obtained and that one must proceed from one step to another in an effort to find the best possible solution to the problem involved in each individual case The degree of maldevelopment is extremely variable, and therein lies the explanation for an improved situation after treatment in some patients and the reason for failure in others

Each individual must therefore be subjected to most careful neurologic and urologic evaluations The findings in the urologic examination of these patients differ from those in acquired lesions of the spinal cord and simple congenital obstructive lesions of the vesical neck in that in the majority of cases the external sphincter is of decreased tone and is incompetent The degree of incontinence will vary from one individual to another Some patients will have total incontinence of urine, others almost complete retention, and still others will have both residual and dribbling

The amount of residual urine is probably the best index to the degree of imbalance between the detrusor muscle and the vesical outlet Accuracy in determining the amount of residual urine is important in selection of the method of management Young[1] suggested that "ascendent" lipiodol is a somewhat more rigid criterion for measuring residual urine than is catheterization Those without residuals should retain no lipiodol at the end of 24 hours In the management of these patients the residual urine must be eliminated in order to protect the integrity of the upper urinary tract and permit sterilization of the urine

Five surgical procedures may be used in the treatment of vesical dysfunction that results from spina bifida They are transurethral resection, retropubic Y-V plasty with posterior wedge resection, the Millin sling operation, the Kelly or some similar type of urethroplasty, and complete closure of the vesical neck with permanent suprapubic drainage Because of the variability of the lesion,

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Read at annual meeting of American Association of Genito-Urinary Surgeons, Hot Springs, Va., May 1–3, 1957

[1] Young, B W, Anderson, W L and King, G G Radiographic estimation of residual urine in children J Urol., 75 263–272, 1956

the application of any method of management to an individual problem is highly selective, and many failures will be encountered In patients in whom all other procedures have been unsuccessful, construction of a substitute bladder from an isolated intestinal segment should be considered

TRANSURETHRAL RESECTION

In patients who have residual urine, transurethral resection of the vesical neck is perhaps the most effective means of establishing a balance between the strength of the detrusor muscle and the resistance of the vesical outlet In the application of transurethral resection to this group of patients, age and sex must be considered The size of the urethra in boys less than five years of age limits the size of the instrument that can be used and therefore the adequacy of the procedure itself Emmett and associates[2] suggested that it is best not to try transurethral resection in boys less than two years of age In this group they recommended suprapubic cystostomy to protect the integrity of the upper urinary tract, and appropriate use of perineal urethrostomy in boys older than this in an effort to prevent urethral stricture

Transurethral resection of this type of lesion is a more meticulous procedure than transurethral resection of simple non-neurogenic congenital obstructive lesions The landmarks are not clearly defined The entire circumference of the urethra should be resected from the internal vesical orifice to the verumontanum, and it is better to remove too little tissue than too much Most of our patients have required two resections and some three or more The operation should be repeated as soon as it can be established that residual urine is still present If as much tissue as possible has been removed from the prostatic urethra, and the patient still has residual urine, resection of the proximal margins of the external sphincter is justified provided one recognizes the narrow margin between residual urine and total incontinence

The female urethra lends itself well to urethral dilatation, which will permit earlier performance of transurethral resection with little likelihood of the subsequent development of urethral stricture Our experience in the management of a large group of non-neurogenic obstructive lesions in females is that in patients older than five years the urethra can usually be sufficiently dilated to permit use of an adult type of instrument The danger of development of urethrovaginal and vesicovaginal fistulas is recognized and the amount of tissue that can be safely removed from five to seven o'clock is limited More liberty may be exercised in the remainder of the circumference, and the posterior third of the urethra may be safely resected By use of transurethral resection it should be possible to eliminate residual urine in this group of patients

THE OPEN RETROPUBIC APPROACH

The difficulty in removing an adequate amount of tissue transurethrally in children of both sexes younger than five years of age has led us to use an open approach with increasing frequency during the past 12 years Enough patients with neurogenic and non-neurogenic lesions have now been followed for a sufficient period of time to evaluate postoperative results In operating upon the neurogenic lesions one is faced with the same problem that exists in the performance of transurethral resection, that is, the entire circumference of the posterior urethra must be included Posterior wedge resection alone did not prove satisfactory After the first report of Young[3] of his modification of the open procedure we started adding it to the posterior wedge resection His Y-V plasty is now being used instead of the original longitudinal incision and transverse closure This has resulted in considerable improvement of the results obtained in the non-neurogenic cases It has been our experience, as well as that of others, that not enough tissue can be removed from the distal portion of the posterior urethra to eliminate residual urine in many cases It has the advantage, however, that it can be performed on children in the age group in which Emmett recommends suprapubic cystostomy Suprapubic cystostomy drainage may be continued and supplementary transurethral resection can be performed when the child is older if removal of more tissue is indicated

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[2] Emmett, J L and Simon, H B Transurethral resection in infants and children for congenital obstruction of the vesical neck and myelodysplasia J Urol , 76 595–608, 1956

Two complications may occur during performance of the open operation One is vesicovaginal or urethrovaginal fistula in females and the other is urinary incontinence from extension of the longitudinal incision too far distally in both sexes An apical stitch should always be inserted but this does not offer absolute protection against development of this latter complication Young[4] suggested that incontinence may occur from tenting of the external sphincter by a longitudinal incision and transverse closure His experience with the procedure in the neurogenic group parallels that of others in that the results are less satisfactory than in non-neurogenic cases

THE MILLIN SLING OPERATION

We have tried to rationalize use of the sling operation in the management of vesical dysfunction due to spina bifida It is contraindicated in patients with residual urine In those with a relaxed external sphincter and no residual urine, it would appear to create an imbalance by increasing the resistance at the vesical outlet This has been borne out by the postoperative course of some of our patients who have had the sling operation An example of this is the case of a girl, five years old, on whom the operation was performed in August 1955 Although she has been able to keep reasonably dry, the intravesical pressure has been sufficiently increased to produce left vesicoureteral reflux The sling operation has been shown to produce enough obstruction at the vesical neck in non-neurogenic cases to cause decompensation of the upper urinary tract, and its use in the neurogenic group should be contraindicated

PLASTIC PROCEDURES ON THE URETHRA

In patients with total incontinence of urine a Kelly type of urethroplasty may be performed to support the action of the external sphincter and improve control This procedure should be reserved for the older girls, in whom the operation is easier to perform than in younger girls A surprising amount of working space can be obtained by performance of a liberal episiotomy An occasionally satisfactory result may be obtained from this procedure but the difficulty lies in securing enough support to prevent dribbling without increasing resistance at the vesical outlet sufficient to contribute to damage of the upper urinary tract Patients treated by either of these latter procedures must be carefully followed

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[3] Young, B W Retropubic approach to vesical neck obstruction in children Surg, Gynec & Obst 96 150-154, 1953

[4] Young, B W Personal communication to the authors

CLOSURE OF THE BLADDER NECK

Gross and associates[5] favored complete closure of the vesical orifice with permanent suprapubic cystostomy drainage only after all other methods have failed The frequency of failures from other methods and the infrequent use of this procedure suggest that it should be utilized more often than it is The catheter may be attached to a small collecting bag or clamped and opened at intervals These patients are usually able to enjoy a reasonable degree of activity Everyone is familiar with the complications of continuous suprapubic drainage but good management should reduce these to a minimum Construction of a substitute bladder from an isolated intestinal segment is being evaluated in a number of medical centers and may prove to be a method of choice in the management of many of these cases

SUMMARY

The variable results of the surgical treatment of vesical dysfunction due to spina bifida are evidence that there is no standard method of management of all cases There are five surgical procedures that may be performed on the dysfunctioning vesical neck due to spina bifida in an attempt to eliminate residual urine transurethral resection, retropubic Y-V plasty with posterior wedge resection, the Millin sling operation, the Kelly or some similar type of urethroplasty, and complete closure of the vesical neck with permanent suprapubic drainage Of these, transurethral resection has been found to be the most satisfactory Operations that increase the resistance at the vesical outlet are contraindicated

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[5] Gross, R E, Holcombe, G W, Jr and Swan, Henry Treatment of neurogenic urinary and fecal incontinence in children A M A Arch Surg, 66 143–154, 1953

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THE ROLE OF SPINAL CORD TRACTION IN THE NEUROVESICAL DYSFUNCTION OF SPINA BIFIDA

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Urinary incontinence, so importunate a result of the neurosurgical correction of the more extensive varieties of spina bifida, has somewhat tarnished the technical brilliance and mitigated many of the benefits attendant upon early meningomyelocele repair Therapeutic disenchantment has stemmed not so markedly from the social stigmata of the incontinence as from a fuller realization of the severity of divestment of sacral cord control of the bladder, and the hazards which may derive from the neurovesical dysfunction so produced

It has been insufficiently appreciated that the incontinence in the surgically corrected meningomyelocele is not solely a matter of a patulous vesical outlet but perhaps more properly a result of a dyskinesia between a malfunctioning vesical detrusor and an incompetent sphincteric area Urinary residuum is frequently pronounced and can lead to the deleterious obstruction-infection sequences which constitute the prime hazard to normal longevity in these individuals

Penfield and Cone[1] in their discussions of spina bifida postulated that skeletal growth subsequent to early meningomyelocele repair might produce traction of the anchored spinal cord and its roots This observation coupled with the sporadic reports of Chute,[2] Mertz,[3] and others that dissection of scar from the nervous tissue in the area of the previous repair was occasionally productive of a return to continence led us to an evaluation of a group of patients who had undergone neonatal meningomyelocele repair and were subsequently incontinent of urine

A preliminary report of the clinical findings in the five patients investigated has been previously made[4] and is a fascinating study of the paradoxical features of the neurovesical dysfunction of the spina bifida group

Each of these individuals had experienced persistent urinary and bowel incontinence subsequent to the neurosurgical reparative procedure Four of the patients were male, aged 26, 19, 14 and 13 years respectively, and one a female aged five years All exhibited saddle anesthesia, absent bulbocavernosus reflexes, and despite varying vesical capacity, cystometric evidence of autonomous detrusor responses to incremental filling All experienced a sensation of vesical distention at individual total bladder capacity but other sensory modalities were absent Digression from clinical similarity existed in urographic findings

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[1] Penfield, W Spina bifidum and cranium bifidum J A.M.A , 98 454–460, 1932

[2] Chute, A L The relation between spina bifida occulta in certain cases of retention J Urol , 5 317–324, 1921

[3] Mertz, H O and Smith, L A Posterior spinal fusion defects and nerve dysfunction of the urinary tract J Urol , 24 41–82, 1930

[4] Thompson, I M , Jackson, I J and Hooks, C A Restitution of continence in spina bifida A.M A Arch Surg , 74 338–344, 1957

and in the presence or absence of urinary residuum The 26- and 19-year-old men had normal upper tracts radiographically, no ureteral reflux, and carried no residuum The other three patients exhibited varying degrees of upper urinary tract dilation and functional deterioration, all had significant urinary residua Cystographically and cystoscopically marked vesical trabeculation was evident in all patients

The first sacral cord exploration was done in the latter part of 1954. During surgery a recording cystometer transcribed no bladder response to electric stimulation in the area of scarring or of intact nerve roots above it The spinal cord was bound down under tension by adhesions and the more cephalad nerve roots were bowed by the traction With release of the cord it moved cephalad several centimeters Postoperatively, the patient noted a gradual diminution of incontinence to the point that with observance of a two hour voiding schedule he remained completely dry To the present time this man has maintained a continent, useful place in society Studies revealed no abnormality of the upper urinary tracts and no urinary residuum Cystometric examinations show a definite change from the preoperative state (fig 1)

Stimulated by this result four patients with a similar history and clinical findings were subjected to sacral cord re-exploration between late 1954 and mid-1955 The five-year-old girl almost immediately became completely con-

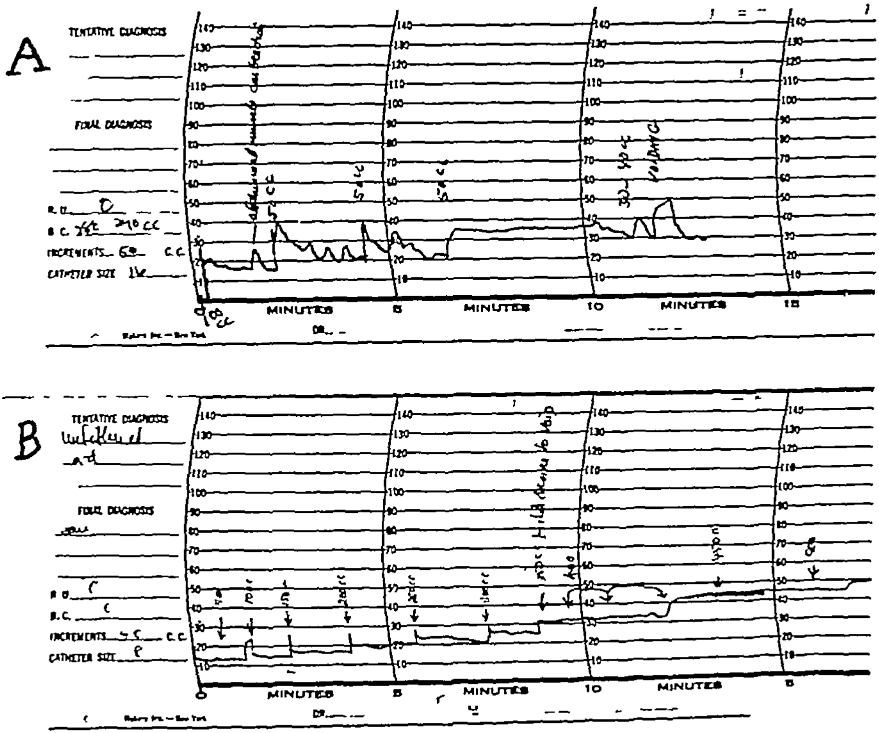

Fig 1 A, pre- and *B*, postoperative cystogram

tinent day and night No change was observed in the amount of urinary residuum nor in the upper urinary tract dilation The 14-year-old boy became more continent, he could remain dry for two-hour periods during the day but was wet at night The 26-year-old man has for nearly three years since surgery maintained continence despite the rigors of his occupation as a traveling salesman His upper urinary tract is normal functionally and radiographically It is now almost two years since exploration in the 13-year-old boy, he has gained increasing urinary control, without any noticeable change in his upper urinary tract status He carries no residuum nor infection

Each of these patients had been plagued by constant dribbling of urine on the slightest exertion In each at surgery the spinal cord was bound down by scar and in none could a cystometric response be elicited by electric stimulation of the scar or intact nerve roots Excision of adhesions led to relief of traction and cephalad migration of the cord in all cases Training in respect to a voiding schedule, the method of Credé and other adjunctive measures was rigorously carried out and resulted not only in an increasing measure of control but in a more forceful elimination of urine

In view of the seeming beneficial effect of the sacral exploration on the micturitive pattern of these five patients we tentatively attributed their more continent status to the release of traction on the spinal cord and its nerve roots Since an intact sacral parasympathetic arc had not at any time been demonstrated, seemingly the sole vesical effect cord release could exert would lie in an obviation of spinal root compression and ischemia and a subtended rejuvenation of the T-12 and L-1 sympathetic nerve supply

As a mechanism for greater detrusor effectiveness postulation of the inception of a sympathetically mediated control appeared tenuous in view of numerous attestations as to the inessential nature of the sympathetic vesical nerve supply Present day concepts of vesical innervation would more feasibly support an assumption that in these patients some type of sacral reflex arc did exist despite our inability to demonstrate it The postoperative change then would be ascribed to the conversion of an incomplete infra-nuclear lesion to a complete one, with the production of an autonomous bladder

Two of the patients, however, during the course of periodic re-evaluation following surgery demonstrated fairly sudden reversions to an incontinent status The five-year-old girl who had almost miraculously remained normally continent for over a year, in a short period of time regressed to complete incontinence, and demonstrated a progression of peripheral neurologic deficit, without notable alteration in her urinary tract picture Similarly but more gradually, the 14-year-old boy became totally incontinent once again The only apparent change in these two patients was the occurrence of a skeletal growth spurt with a marked increase in height The reappearance of incontinence following spinal skeletal elongation seemingly denoted a return of spinal cord traction due to a retethering of the spinal cord at the site of the previous lysis Although further surgical exposure did not appear warranted to conclusively establish the validity of this explanation, no other assumption seems reasonable Full skeletal growth had been achieved by the 19- and 26-year-old men, and no further growth had occurred in the 13-year-old boy, and they remained continent

In view of these findings theoretical reassessment of the mechanism of the continence achieved subsequent to the release of a tethered spinal cord leads to the inference of a sympathetic nerve influence If the bladders in these individuals were not totally denervated in respect to parasympathetic supply before the operative scar lysis, of necessity they were subsequent to it Autonomous myogenic vesical control should seemingly remain unmodified by any retethering of the spinal cord yet a change in vesical function and continence as well as a peripheral neurologic deficit reappeared concomitant with a spurt in skeletal growth An assumption that cord traction was thus re-instituted seems plausible and possibly implicates the sympathetic thoracic outflow in the ameliorative change from incontinence following relief of cord traction Under these conditions a new sympathetic reflex arc for vesical control can ostensibly be promulgated with the subtended implication that the sympathetic nervous system may not be totally inessential to vesical function under abnormal conditions

Obviously, sacral exploration of previously repaired meningomyeloceles is no panacea even for so numerically limited a group of incontinent individuals The urinary bladders in these patients are not normal postoperatively but they do appear to be more suitable for social rehabilitation and perhaps physiologically more competent From this study it would appear that the spinal cord untethering procedure warrants further investigation but should await near maximal skeletal growth to avoid a subsequent recurrence of traction

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THE MANAGEMENT OF THE SPASTIC BLADDER IN PARAPLEGIA

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The best treatment of any dysfunction is prophylactic In the light of current knowledge and practice, it may be expected that 75 per cent of patients with paraplegia or quadriplegia due to spinal cord injury will achieve satisfactory function of the urinary bladder with adequate capacity, reasonably good control, and no need for adventitious drainage (Comarr, Talbot) Of the remainder, a variable proportion, depending upon a number of factors, will exhibit the so-called spastic bladder This is a general term embracing several recognizably distinct dysfunctions, individually or in combination In some instances it is probably not strictly accurate in a physiological sense Semantics apart, it is none the less essential to consider the genesis of these manifestations as a prerequisite to a discussion of their management

The spastic bladder has definite functional and structural characteristics Its capacity is diminished, and there are frequent emptying efforts, because these are often ineffectual, residual urine is commonly found The intravesical pressure is consistently elevated In consequence of this abnormal activity the muscle of the bladder wall becomes hypertrophied and trabeculation develops Eventually the bladder becomes markedly contracted, the result of sustained muscular activity alone, or, more frequently, in association with fibrosis In the latter event the structural alteration may be irreversible This is not an inevitable end stage in the evolution of the bladder after spinal cord injury It may have been that in years past, but in modern practice it is an anachronism to accept it as such In some instances, however, it still occurs, and it becomes necessary to seek out the causes of this unsatisfactory outcome

Since this is not a description of the neurophysiology of micturition, it must suffice to state that there seem to be certain primary neurogenic factors in the causation of spasticity of the bladder which are implicit in many cases of spinal cord injury Various explanations of this phenomenon have been offered, only a few of which need be mentioned here It has been pointed out that the maintenance of tonus by the bladder is at least in part a myogenic activity Indeed there are those who insist that it is entirely myogenic (Tang and Ruch) It seems more rewarding, however, to think in terms of a neuromuscular apparatus, with the neural elements contributing a significant element of integration and modulation of the complex activity whereby the bladder wall adapts itself to its content with such extraordinary precision and, at a given point of fill, discharges that content smoothly and efficiently (Bors, Talbot, Tang) Myogenic activity may become excessive when neural control is impaired, and spinal reflex activity may increase when deprived of modulating influences from higher centers The loss of efficiency calls for greater effort for expulsion, and abnormally high intra-

Read on July 25, 1957 before Paraplegia Section of 7th World Congress of International Society for Welfare of Cripples, held in London, England vesical pressures develop, this results in hypertrophy, which, in turn, leads to further hyperactivity The lesion itself, acting as an irritant, may reflexly stimulate activity in excess of that normally evoked by the usual stream of afferent impulses into the spinal reflex centers In the case of a complete transection, this may be apparent only after the period of so-called spinal shock has passed It is perhaps more evident in those instances in which the spinal cord is the site of patchy incomplete lesions, such as are encountered in the early stages of multiple sclerosis (Muellner, Talbot) Micturitional dysfunction is commoner, early in this disease, than is ordinarily recognized, and usually takes the form of heightened activity, manifested by frequency, urgency, and diminished capacity

Of no less importance, clinically considered, are certain other factors which are superimposed upon the neural components Almost all these patients require catheter drainage, and the irritating presence of the catheter is itself a stimulant to increased bladder activity Infection almost invariably follows, another irritating agent of great importance, the effect of which is in some instances enhanced by the presence of encrustations or bladder stones Urethral complications are common, particularly urethritis, periurethral abscess, and fistulas These may provoke powerful stimuli to detrusor activity Parenthetically, however, it is interesting to observe that infections in the genital passages ordinarily have the opposite effect, the commonest of these, acute epididymitis, will frequently impede if it does not entirely inhibit effective contraction of the bladder wall Hypertrophy of the detrusor muscle involving that portion which constitutes the bladder neck may become so marked as to cause obstruction, which is increased in the presence of infection by the consequent fibrotic changes To overcome this, the detrusor must compensate by further hypertrophy and hyperactivity

Extravesical factors may also play a part Severe skeletal muscle spasm involving the lower extremities and the lower portion of the abdomen causes changes in intravesical pressure which, when sufficiently marked, may stimulate contraction of the bladder wall This sometimes causes stress incontinence with bladders otherwise conditioned to a satisfactory type of reflex activity What is worse, it may involve such frequent stimulation as to make satisfactory conditioning impossible, and, in conjunction with other factors, contribute to the development of a truly spastic bladder Vesical activity in such instances does not seem to be part of a mass reflex but, rather, a secondary phenomenon Cystometric observations indicate that the bladder contraction does not occur simultaneously with the spastic movements of the skeletal muscles, but only after a latent period during which the intravesical pressure rises to a level sufficient to initiate activity (Talbot)

In all this there is repeated evidence of the constant reciprocal relationship between function and structure (Talbot) Altered patterns of activity induced by neurogenic dysfunction result in compensating structural alterations, such as hypertrophy, or indirectly induced changes such as those which result from infection By the same token, structural changes of whatever origin express themselves in disturbed function Since the urinary bladder adapts itself so accurately to its content, it will, after prolonged and continuous drainage through a catheter or suprapubic tube, be found to have adapted itself to a content of zero, and become permanently contracted. Even in the total absence of infection, which is unfortunately hypothetical, or when infection can be fairly effectively controlled, which is frequently possible, this configuration is maintained by muscular activity. Under such circumstances, the situation may still be amenable to correction. With active infection, however, the subsequent fibrosis may render the structural changes irreversible, and any improvement in function becomes impossible simply because the end organ is no longer capable of suitable activity. Such a bladder, even when there are no other influences which might provoke excessive activity, will, in its end state, simulate spasticity. It is axiomatic, therefore, to recommend that artificial drainage of any kind be discontinued as soon as possible, or, if it must be prolonged, that shrinkage of the bladder be prevented by tidal drainage or any other maneuver providing for rhythmic filling and emptying. Unfortunately, even this may be impossible. The development of ureteral reflux may at times, although not inevitably, make any accumulation in the bladder undesirable. Autonomic hyperreflexia, a common phenomenon in high dorsal and cervical transections, may manifest itself by the development of dangerous levels of hypertension in response even to minimal distention of the bladder. Moreover, this is prone to occur in precisely those cases in which there is already a tendency toward vesical spasticity. The result is an impasse unless something can be done to break the vicious cycle (Guttmann and Whitteridge, Pollock and associates, Schumacher and Guthrie, Thompson and Witham).

Turning to actual management of the spastic bladder, the discussion must begin by reverting to the theme of prophylaxis. Before considering what can be done for those patients in whom it has already occurred, it is appropriate to refer briefly to the means of avoiding it when that is possible. When the spinal cord lesion is cephalad to the conus, i. e., an upper motor neuron lesion, sparing the sacral segments in which the spinal reflex centers for micturition are located, there is a good chance, all other things being equal, of achieving satisfactory bladder function. Already described elsewhere, this is accomplished by insuring adequate drainage from the outset so as to avoid over-distention, followed by conditioning of the reflex activity, the earliest possible removal of the catheter, and habit training. It has been pointed out that at times this result may be obtained without any elaborate process of bladder training, and it is no doubt true that many patients can manage it on their own. None the less, there are few who will not be the better for some guidance and instruction, and the development of a consistently behaving reflex bladder through a reasonable period of tidal drainage provides a sound background for the establishment of good micturitional habits (Bors, Comarr, Talbot). Maintenance of good general health, avoidance of infection, and appropriate steps to reduce the incidence of renal calculus formation are important concomitants. When obstruction at the bladder neck occurs, it should be corrected by transurethral resection (Comarr, Emmett, Albert and Anderson). On occasion a successful issue may be impeded by localized spasm of striated muscle elements in the sphincter mechanism. For the most part, these consist of the deep transverse perineal and bulbocavernosus muscles which, in effect, constitute the external sphincter Bors, Comarr, and Reingold have also described striated muscle fibers intermingled with the smooth muscle of the anterior portion of the bladder neck (Bors, Comarr and Reingold) Such spasm may be corrected by pharmacologic block or surgical interruption of the pudendal nerves (Bors, Comarr and Moulton, Bors and Comarr)

When spasticity is already present the first problem is to determine how it came about—which of the mechanisms already described operated in its development If none of the primary factors was responsible, and if there is no impediment to establishing a program of bladder conditioning, the solution of the problem will lie in the correction of those secondary or extraneous influences which may be present In actual practice, this may be a difficult and time-consuming process, and a description of all the urologic procedures involved would be beyond the scope of this discussion In most instances, however, it can be successfully accomplished even when there are multiple complicating elements A satisfactory result, naturally, will depend upon the degree to which structural changes are compatible with resumption of good function The last point is of particular importance in those cases in which bladder spasticity is associated with ureteral reflux The changes in the ureteral wall in such a situation may or may not be susceptible of regression If infection can be controlled and adequate drainage established, the ureter may effectively compensate even for some degree of permanent damage With such compensation, reflux manifesting itself simply as a roentgenographic finding, with no evidence of renal damage or impairment, *is not a contraindication to termination of catheter drainage and efforts to establish* a good pattern of reflex micturition Continued vigilance, of course, is necessary in such cases

The association of spasticity of the bladder with autonomic hyperreflexia is, unfortunately, quite common Both may be direct manifestations of neurogenic dysfunction, but in many cases, and probably to some degree in all, the bladder contracture is a consequence of the necessity for continued drainage Attempts to distend such a bladder, even with no more than an ounce or two of fluid, may provoke elevations of the blood pressure to a level as high as 250 systolic over 140 diastolic In some instances this stimulus is elicited not only from the bladder but from the urethra, and any type of manipulation, even a simple catheter change, is attended by this dangerous response A number of methods for controlling such hyperreflexia have been proposed and attempted, including extensive anterior and posterior rhizotomies (Bors and French) In recent years a considerable success has been achieved in a large number of patients by the use of the so-called ganglionic blocking agents, particularly hexamethonium and ansolycin (Kurnick) The dosage is not always easily established since it must be developed empirically for each patient Carefully managed, however, this conservative method has been reasonably effective Unfortunately, many patients who are symptomatically relieved are not benefited to a degree permitting removal of the catheter In these, the reflex can be interrupted by blocking or division of the sacral roots A successful block will generally last considerably longer than the anticipated pharmacological effect, usually from) 24 hours the first time it is done, and for longer intervals on succeeding oc- ons In a number of cases it has been possible to space these blocks as far as months apart, and in such circumstances, considering the simplicity of the cedure, surgical interruption is probably unwarranted In those instances, vever, in which the block has only a temporary or an inadequate effect, zotomy or neurotomy must be considered (Bors, Comarr and Moulton, eibert)

t might be noted, while discussing the efficacy of these procedures in the itrol of autonomic hyperreflexia, that sacral blocks were originally used to dify spasticity of the bladder, and the effect on the hyperreflexia was a grati- ng secondary observation Similarly, the surgical approach, whether by ral neurectomy or rhizotomy, was originally directed at the improvement of dder function (Brendler and associates, Meirowski and Scheibert) The fact iains that at the present time the major value of these procedures may lie in ir control of the generalized autonomic reactions rather than the localized ceral disorder Certainly there is no warrant for using sacral rhizotomy in- criminately in the hope of restoring satisfactory micturition In carefully ected cases, where there is persistent hyperactivity after all other contributing tors have been controlled as far as possible, there may be a sound indication some such procedure As the operation is performed, not all of the sacral roots divided in every case When only the third and fourth are divided bilaterally, effect is substantially that of pudendal nerve interruption, abolishing spasm the striated muscles of the external sphincter while leaving the detrusor sup- ed from the second sacral segment When the second, third, and fourth roots divided on both sides, the detrusor has theoretically lost its entire efferent iervation with the exception of a few sympathetic fibers which supply the gion of the trigone and the bladder neck This would effectively abolish de- isor spasticity of reflex origin, but leave the emptying of the bladder to depend on any other type of stimulus sufficient to provoke contraction

Most of the patients who have benefited from this procedure initiate micturi- m by a rather vigorous Credé maneuver There may be justification for creating ch a situation, but the indications are probably limited In most cases other ethods of management will be adequate, provided that the structure of the adder has not been irretrievably damaged Anterior rhizotomy undertaken for lief of skeletal spasm, with preservation of the roots that provide the innerva- on of the detrusor, may be followed by improvement of previously unsatis- ctory bladder function This is an indirect effect, representing control of an traneous factor which has contributed to hyperactivity, but in any given case may be of decisive influence Excellent results have also been achieved by ie alternative, less selective, procedure of subarachnoid alcohol block, which icludes the sacral outflow The fact, however, that relief of hyperactivity of the ladder may follow, even when its nerve supply has been spared, suggests that enervation is not indicated in every instance, and not before an attempt to ring other contributory factors under control

The general scheme of attack on the problem of bladder spasticity may thus be recapitulated

First, avoidance of the type of drainage which results in contracture

Second, control of the secondary and extraneous factors already mentioned, and correction of structural alterations The problem is thus reduced to terms of the primary neurogenic dysfunction which can, in many instances, be adequately managed by conditioning of the reflex micturitional function and habit training

Third, when such conditioning is unsuccessful, there may be indication for a direct attack on the neural pathways to the bladder by pharmacological block or surgical interruption

All of this assumes that the end organ has remained capable of acting effectively But when the bladder itself is hopelessly beyond any type of retraining, even with the aid of ancillary surgical procedures aimed at improving its structure or modifying its nerve supply, when, in spite of the correction of all recognizable contributing factors, it remains an incubus rather than a useful organ, consideration must be given to the possibility of diversion or reconstruction This is not simply a matter of providing the patient with a convenient method of urinary drainage, but rather, in the instances now under consideration, an essential step in salvaging the urinary tract For by this time the upper tract will almost inevitably have become involved, usually with hydroureter, hydronephrosis, pyelonephritis, and possibly impairment of renal function This may be further associated with bouts of intermittent hypertension and other autonomic disorders

Major mutilating procedures with irreversible results, carrying a significant morbidity and an appreciable mortality, are not justifiable save in the presence of such cogent indication In most instances conservative methods of management, with such operative intervention on occasion as has already been mentioned, will be successful As experience accumulates and understanding broadens, one may hope that fewer patients will reach the sorry stage at which nothing can be done with the bladder except to get rid of it Unfortunately, a certain number do reach this stage, *and for these, if only for these, it is essential to provide some* substitution of function The variety of procedures recommended at one time or another for urinary diversion or bladder replacement is so great as to suggest that none has been found entirely satisfactory This is perhaps a further argument against their indiscriminate application As regards diversion, the choice is limited, in the patient with spinal cord injury, by the associated bowel dysfunction which excludes any kind of ureterocolonic anastomosis Since this is not the place for discussion of all methods available, reference will be made only to the one employed in the series of cases on which this study is based This is the cutaneous ureterostomy through a pedicle flap which has been generally satisfactory, granting that no method of urinary diversion is likely to rise above the status of an improvisation (Talbot, Paull and Read) It has been done in 6 paraplegic or quadriplegic patients out of a total of 700, and there were 4 others, two of whom have since died, to whom the operation was recommended but who refused it This may serve as an estimate of the frequency with which it seemed indicated

Many ingenious methods of bladder substitution have been proposed, which have been useful in other types of patients, but seemed not to meet the special needs of those in this series, either in terms of the dysfunction to be corrected, or the background of the patient's general condition It was not until this year that the first such operation was performed on any of this group of 700 The method chosen was the reversed sero-muscular ileal graft developed by Shoemaker and Long, which has the advantage of providing a new detrusor element which retains not only its vascular but its neural supply (Shoemaker and Long) The patient has done well and the ileal bladder 6 months after operation shows a definite and continuing improvement over the original Of particular interest is the fact that episodes of hypertension previously provoked by bladder distention no longer occur There is a residue of autonomic hyperreflexia in the form of sweating, but this seems to be stimulated more by irritation of the urethra and the trigonal area than by the newly constructed bladder wall It is too early to draw any conclusions from a solitary case, but it may at least be hoped that this method will be available for the relief of patients whose bladders have reached a stage at which nothing else can be done

SUMMARY

Spasticity of the bladder in paraplegia and quadriplegia may represent a primary, purely neurogenic dysfunction More commonly, however, it is the result of the interplay of a number of factors superimposed upon this

The functional disorder provokes secondary structural alteration which may, in turn, contribute a further element of dysfunction

Prolonged continuous catheter drainage, leading to shrinkage of the bladder, may simulate or enhance true spasticity

Management involves prevention or correction of structural changes, elimination of the secondary and extraneous contributing elements, and the reconditioning of the reflex activity of the bladder in the hope of correcting the neurogenic dysfunction If this is unsatisfactory, the neural activity may be modified by appropriate nerve block or surgical interruption

When the bladder is irreversibly altered, so as to be incapable of any resumption of satisfactory function, recourse may be had either to diversion or to some form of bladder substitution

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PATENT URACHAL CYST

EUGENE S FELDERMAN AND THEODORE R FETTER

From the Department of Urology, the Jefferson Medical College Hospital, Philadelphia, Pa

Diseases of the urachus are uncommon enough to warrant reporting a single case In a survey of 15,000 admissions to the Brady Urological Institute only three cases were concerned with diseases of the urachus Only three cases were found in 200,000 admissions to the Children's and Infants' Hospital of Boston Survey of reported cases in the literature up to and including the year 1950 totaled 192 cases In reviewing the literature, Sterling and Goldsmith in 1953 were able to collect only 26 proven cases of urachal tract disease in which symptoms and signs appeared after the age of five years Twenty-one cases were observed between the ages of 8 to 20 years Only three appeared over the age of 51

Embryologically the urachus represents the vestigial remnant of the allantois which, in the fetus, communicates with the cloaca Originally the bladder proper is tubular, but after the second month, it expands into an epithelial sac whose apex tapers into an elongate urachus The urachus in turn is continuous at the umbilicus with the remnant of the allantoic stalk After birth, the urachus is drawn downward by the descending bladder The whole complex is known after birth as the middle umbilical ligament Begg is of the belief that the urachus is embryologically a portion of the bladder and that both develop from the ventral cloaca as a single, hollow viscus The structure is lined by transitional epithelium

The most common cause of urachal disorders is due to a developmental failure of obliteration With the entire tract patent, urine will be found to drain from the umbilicus With both ends closed, a blind cyst develops and, in addition, either the umbilical or vesical end may fail to close It is understandable that in the former, i e , the blind pouch, little or no difficulty will occur unless infection should intervene Urachal disease would seldom be discovered unless umbilical drainage is encountered or an inflammatory mass appears at the umbilicus It is noteworthy, also, how infrequently primary symptoms are the presenting complaint Very few cases have been reported over the age of 50 All cases reviewed were symptomatic, again, the most common symptoms being those of infection Complications include abscess, granulomas and tuberculosis, urachal calculi have been reported An infected cyst may rupture intraperitoneally, intravesically or into the bowel Neoplastic changes may occur, either benign or malignant An example of the former is the colloid cyst Hayes and Segal in 1945, after reviewing the literature, reported 45 cases of carcinoma of the urachus, including a case of their own

CASE REPORT

The following case report is that of a male patient who had no symptoms referable to urachal tract disease per se He was hospitalized for relief of symptoms

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of prostatic obstruction and the diagnosis was established following cystography

J R, a 55-year-old Negro, was admitted to Jefferson Hospital with symptoms of vesical neck obstruction of at least two years' duration The patient stated that he had gonorrhea at the age of 19 Physical examination was noncontributory with the exception of a symmetrically enlarged prostate, 1½ times normal size

Laboratory data revealed a normal hemogram Microscopically, the urine was found to be infected Staphylococcus aureus was subsequently cultured The blood urea nitrogen, creatinine, and fasting blood sugar were all normal The blood Wassermann was negative The patient was placed on catheter drainage, because of finding 175 cc residual urine A subsequent phenolsulfonphthalein determination was 40 per cent in 30 minutes

Intravenous urography four days after admission revealed a markedly trabeculated bladder, a few diverticula and very minimal upper tract changes, secondary to bladder neck obstruction (fig 1)

Cystoscopy revealed a heavily trabeculated bladder with many cellules and several small diverticula There was elongation of the prostatic urethra due to trilobar hypertrophy Two days later cystography showed, in addition to the diverticula, an irregular, pouch-like structure extending cranialward from the anterior, superior portion of the fundus of the bladder (fig 2, *A* and *B*) There was complete emptying of this structure when the bladder was drained

Subsequently, the patient was taken to the operating room and under spinal anesthesia, cystoscopic examination was repeated It was not possible to view

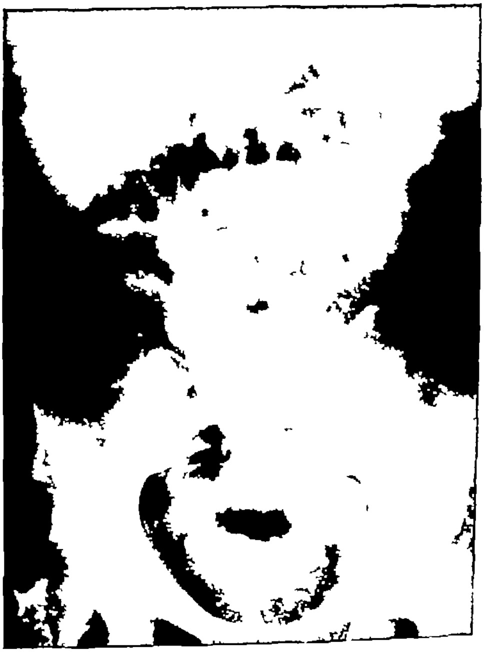

FIG 1

the orifice of the urachal structure because of overlying mucosa Through a midline, suprapubic incision the bladder was mobilized, opened and the cyst-like structure was excised along with a cuff of the bladder The umbilicus was sacrificed Because of adherence of the posterior cyst wall to the anterior parietal peritoneum, this was removed with the specimen Suprapubic cystostomy drainage was employed

The patient had an uncomplicated postoperative course and eight days later transurethral resection of the prostate was performed Eleven days later the patient was discharged The suprapubic sinus was closed and he was voiding without difficulty

The specimen measured 8 5 cm in length and consisted of a cuff of bladder and the umbilicus (fig 3, A) The ostium was found to measure 0 8 cm in diameter There were no mucosal irregularities or valves present on the cut section

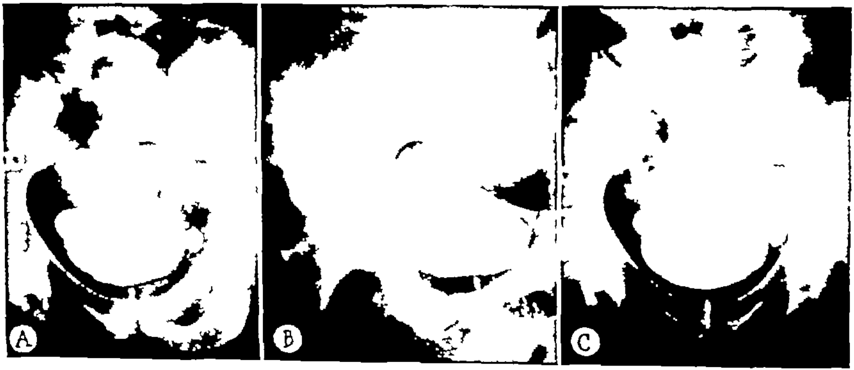

FIG 2

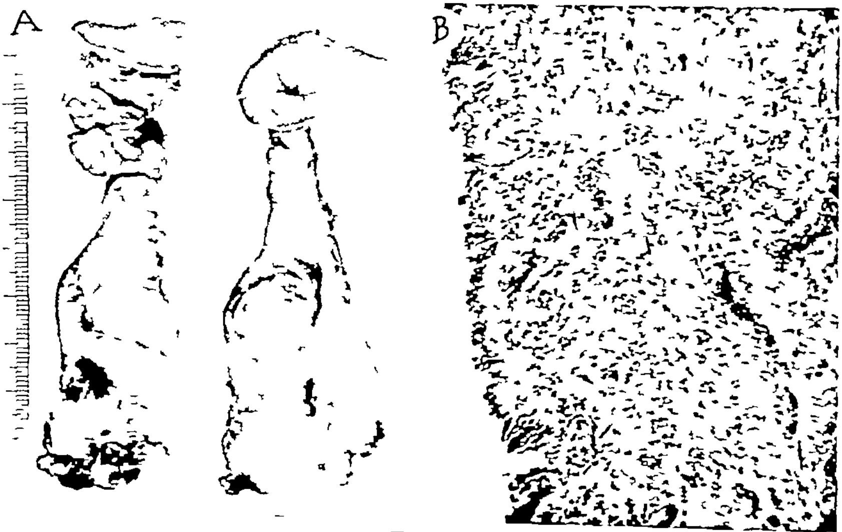

FIG 3

Microscopically, the cyst was lined with transitional epithelium (fig 3, *B*) The prostatic tissue revealed benign hyperplasia

Cystography performed three months following surgery demonstrated an excellent postoperative result The patient remains symptom free 17 months following surgery

COMMENTS

This presentation illustrates the following interesting features

Paucity of cases discovered in patients over the age of fifty The majority of reported cases have been in children under the age of five years

The perchance discovery of the urachal structure following cystography and subsequent difficulty in attempt to completely reproduce filling of the cyst (fig 2, *C*)

Inability to visualize the ostium cystoscopically even after the diagnosis was evident by means of cystography

Complete absence of symptomatology or physical findings referable to urachal tract disease even in the presence of infected urine due to prostatic obstruction

CONCLUSIONS

To the best of our knowledge, this is the first case of a successfully treated patent urachal cyst in a patient without symptoms referable to this structure Had not the patient sought medical attention when he did, subsequent infection and allied sequelae would most certainly have developed This case also illustrates the value of the cystogram in establishing the diagnosis and the absence of positive cystoscopic findings even after the x-ray diagnosis was evident

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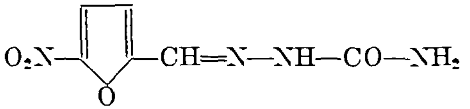
USE OF FURACIN IN TREATMENT OF TESTICULAR TUMORS A CASE REPORT

VICTOR A POLITANO,* GUY W LEADBETTER AND WYLAND F LEADBETTER

From the Urologic Service, Massachusetts General Hospital, Boston Mass

The first clinical report on the use of nitrofurans in the treatment of testicular tumors was by Wildermuth[1] in 1955 Furacin was used to treat a patient with extensive pulmonary metastasis from embryonal cell carcinoma with complete regression He was without clinical evidence of disease one and one half years later At autopsy two years later, the lungs showed scars throughout with no evidence of tumor at the sites estimated as being points of previous metastatic disease The brain showed extensive metastases of choriocarcinoma[2] Friedgood, Danza and Boccabella treated 4 cases of seminoma[3] They reported marked degeneration of the tumor cells, increased fibrosis and decreased cellularity of the tumor

Furacin (5-nitro-2-furaldehyde semicarbazone) is a furan derivative with the following structural formula



Green and Friedgood[4] studying the effects of nitrofurans on bacterial metabolism noted that furacin, when administered subcutaneously, delayed the growth of mouse sarcoma Prior and Ferguson[5] in an effort to find a chemical cancericidal agent studied the effects of a nitrofuran on the testes of rats Their studies revealed that nitrofurans exert a more specific degenerative effect upon the testicular germinal epithelium in the rat than could be produced with nitrogen mustard This drug had no apparent effect on other organs except the adrenals These pathological changes corresponded to the exhaustion phase of the adaptation syndrome as described by Selye[6] These observations led to the clinical use of furacin in carcinoma of the testicle

The dramatic and almost miraculous clearing of the metastatic lesions in the case reported by Wildermuth encouraged us to use this drug in a patient with seminoma of the testes

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* Present address Department of Urology, Duke Hospital, Durham N C

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CASE REPORT

A G —At age 29 this Argentinian was found to have a tumor of his left testis which was removed There was no node dissection The pathological report was seminoma Six years later pain developed in the right testicle Biopsy showed seminoma The testicle was not removed Deep radiation therapy was given as follows—3,300 r over both inguinal regions, 3,600 r over the great vessels, 3,000 r to the mediastinum and 2,000 to the supraclavicular areas

His first admission to this hospital was in April 1955, because of metastatic disease The essential physical findings were radiation discoloration of the skin over the sternum and abdomen, and absence of the left testis The right testicle was enlarged, tender, hard but smooth No nodes were palpable The hemoglobin was 14 6 gm and white cell count 6,500 The urine was negative Chest x-ray showed some thickening of the soft tissues in the retrosternal region Intravenous pyelograms showed a normally placed left kidney and ureter Moderately severe hydronephrosis was present on the right side The right kidney and proximal ureter were displaced laterally Cystoscopy and examination under anesthesia revealed a normal bladder A mass of nodes was felt on the right pelvic wall Biopsy of these nodes showed metastatic carcinoma consistent with seminoma

The patient refused orchiectomy He was given radiation therapy by super voltage technique and received a tumor dose of 3,000 r This was applied to the inguinal, pelvic, testicular and para-aortic regions

His second admission was in April 1956 During the interim metastatic disease to the lungs developed for which the patient received an unknown amount of radiation to the lungs

Of significance on physical examination were the severe radiation changes of the skin over the chest and palpable masses in the right pelvis His urine, blood studies and intravenous pyelograms were normal X-ray of his chest showed extensive fibrosis but no demonstrable tumor An orchiectomy was performed The pathologic report read "radiation-fibrosis no evidence of malignancy " Supervoltage (2,400 r) to the right lower abdomen was prescribed

The patient was admitted for the third time approximately one month later, complaining of difficulty in breathing On examination his temperature was 99F Tubular breath sounds were present over the lungs The remainder of the examination was essentially as on the first admission A chest film showed progression of the changes described as irradiation fibrosis with pneumonitis He improved rapidly on antibiotics and was discharged 3 days later

His fourth and final admission was a month later He complained of persistent shortness of breath His chest findings were as on the previous admission The pelvic masses were no longer palpable An x-ray of his chest showed a discrete rounded mass in the left lower lung measuring about 6 cm in diameter Superimposed upon the right second rib anteriorly was a small rounded density Elsewhere in the lungs were other suspicious shadows The left diaphragm was elevated, partially obscuring the heart shadow, and involvement of the pericardium could not be ruled out (fig 1) An electrocardiogram showed a sinus tachycardia His dyspnea progressed, requiring oxygen therapy In view of the severe radiation changes present it was the consensus of the Radiation Department that further treatment should not be prescribed On his ninth hospital day he was started on furacin 0 5 gm 4 times daily Three days later this was reduced to 1 5 gm daily because of nausea and vomiting Over the next 15 days he received 24 5 gm The patient improved symptomatically but it was necessary to discontinue the drug because of severe peripheral neuritis involving the arms hands, legs and feet This persisted without improvement

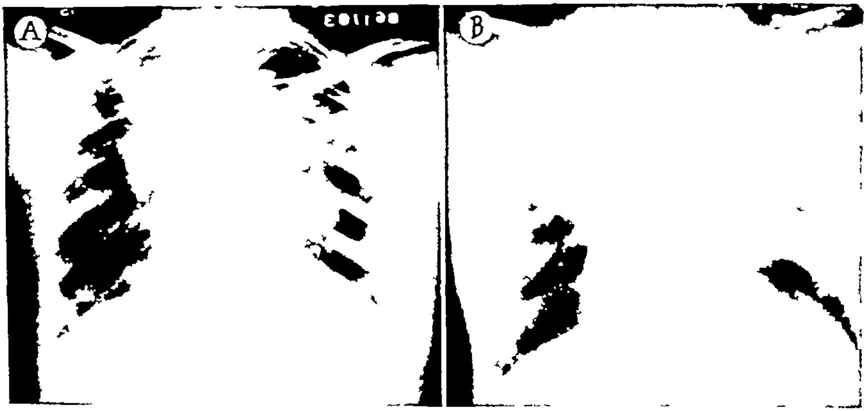

FIG 1 A, x-ray film of chest prior to treatment B, chest film 5 weeks later shows increase in size of metastatic lesions

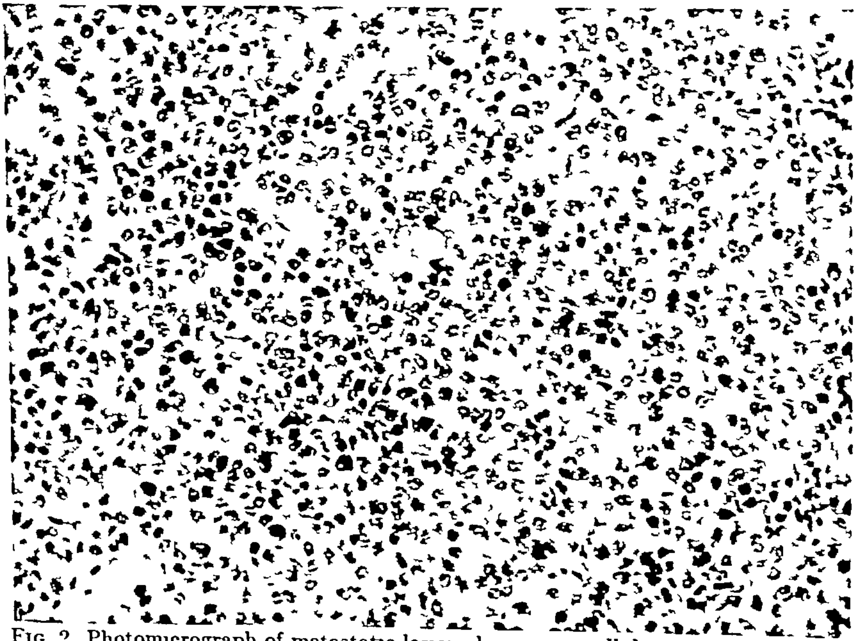

FIG 2 Photomicrograph of metastatic lesion shows monocellular structure made up of rounded polyhedral cells

in spite of daily intramuscular injections over the next 22 days of crude liver extract and vitamin B complex Another chest film showed an increase in the size of the lesions previously noted (fig 2, *A*) His condition did not improve and he expired 10 days later

Postmortem examination showed gross metastatic involvement by seminoma of the bladder, the pelvic, inguinal and mediastinal lymph nodes, the lungs bilaterally, the mesentery and liver (fig 2, *B*)

DISCUSSION

It is generally accepted that the treatment for seminoma is orchiectomy and radiation therapy Sauer and Burke[7] reported a cure rate of 69 3 per cent, Dean,[8] 54 per cent and Lewis,[9] 88 per cent of cases thus treated These are impressive percentages of cure-rates for malignant disease, however, there remains a group of patients, between 12 and 46 per cent, in whom this form of therapy alone was not successful in effecting a cure The outlook for embryonal cell carcinoma is not nearly so good The 5-year survival rate is probably less than 30 per cent The specific degenerative effect of nitrofurans on germinal epithelium suggests that these drugs may be of value in the treatment of embryonal carcinoma It is in this unfortunate group of patients that a drug such as furacin may be beneficial

The purpose in presenting this case report is twofold 1) to call attention to a drug that may prove to be cancericidal for testicular tumors, particularly for seminomas that do not respond or have reached maximum benefit from radiation therapy, and 2) to emphasize that severe neuropathies may occur from such a chemotherapeutic agent Our patient improved subjectively while on medication It is conceivable that he may have improved clinically, were we able to continue the furacin over a longer period Severe peripheral-type neuritis developed, as in the case reported by Wildermuth The neuropathy is thought to be reversible and may be a small price to pay for a "cure "

SUMMARY

A case of seminoma of the testis with extensive metastatic disease, unsuccessfully treated with furacin, is presented

Furacin produces extensive degenerative changes in testicular tissue which is the rationale for such therapy

Severe peripheral neuritis may develop with the prolonged use of this drug

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A SCREWLESS FILIFORM FOLLOWER

DIOMEDE PETILLO

Few urological instruments can equal in ingenuity and usefulness the threaded catheter (Philips, Le Fort) and being an instrument of emergency adds enormously to its indispensability in any case of difficult urination or acute retention due to strictured urethras

However, in the common experience of every practitioner, there are some inherent flaws in the construction of the threaded catheter and its maneuverability that make the instrument cumbersome and, at times, dangerous

The instrument is cumbersome because to thread the screw to the filiform is, in itself, an annoying and time-consuming procedure If, for instance, to attain its initial engagement, the filiform is turned more than one line of the thread, it tends to spiral into the urethra and the follower refuses to slip safely in This is particularly true in all cases of tortuous or very narrow strictures Again, should the screw or the filiform's thread become per adventure only slightly coarse, the screwing would be a trying or impossible procedure and the operator would be compelled to change either the follower or the filiform or both, at the risk of overtaxing his patience in a technical endeavor that requires, before everything else, the utmost of human patience

It is dangerous because during catheterization, in order to gain the prostatic curve, the follower, in a simultaneous move, must be pushed in and pressed downward thusly creating a dynamic set-up that may be responsible for that most feared accident which is the breaking of the minute screw and the release of the filiform into the bladder What really happens here is that the follower's tip carrying the screw, plus the rigid segment of the filiform to which the screw is attached, forced as they are against the anterior wall of the urethra and the anterior lip of the neck, are automatically transformed in a fulcrum-like point of leverage by which the tiny tenure of the screw may be submitted to such an unbearable pressure as to cause its cracking The mishap has occurred much more frequently than one would suspect

Another drawback derives from the vicious angulation to which the most vulnerable segment of the filiform is subjected during the maneuver This angulation disrupts and weakens the fabric of the filiform so as to make its further use bungling and hazardous

In considering these inconveniences I was led to the construction of a screwless follower that in my hands proves to be a safe and serviceable instrument both as a catheterizer and a dilator

THE FOLLOWER

Size, shape and calibration are the same as an ordinary Le Fort's, the only substantial difference being that its tip, instead of carrying the screw, remains

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open barely to allow the passage of a size 5F filiform A minor feature of the follower is a short outlet emerging from its ventral aspect at about one and a half inches from its distal extreme that permits the escape of urine perpendicularly into the basin or into the drum of the examining table

The follower is part of an outfit of 8 units in even numbers from 12 to 26F

THE FILIFORM

This filiform, 26½ inches long, is of the woven type and constructed in three different calibers to fulfill three different functions

The proximal segment, destined to pass the stricture and enter the bladder, has an initial caliber of 3 or 4F and a length of 23 inches This segment is followed by a second one only half an inch long with a caliber that has been gradually and gently increased to reach 6F Carrying a colon band, it acts as a signal to the operator that the filiform has well entered the bladder cavity and as a stopper against the small aperture of the follower's tip The third segment, 13 inches long and 5F in caliber, is destined to enter the follower and run through the entire length of its lumen Its function is to impart and assure continuity between the follower and the rest of the filiform during the latter's guidance and so to make of the two parts one undivided functional instrument

An important feature of this filiform is a central core of silver wire that runs from its distal extreme A to point C of its proximal segment While re-inforcing the fabric of the filiform, this wire enhances its resiliency, adds to its durability

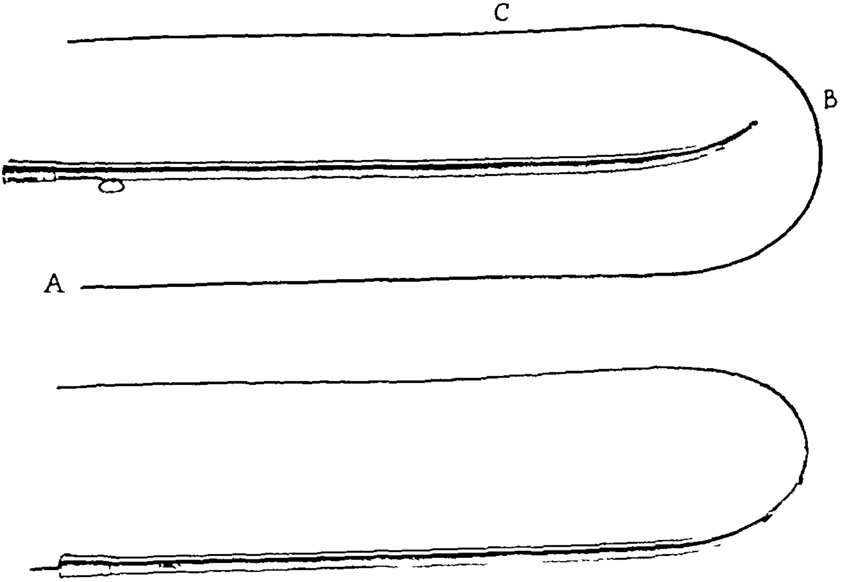

Fig 1

and what is more important, reassures against the possibility of its breaking at the point of its angulation

MODUS OPERANDI

With the patient in proper position the filiform is passed through the stricture into the bladder until the color band rests just out of the external meatus

Now with the follower in the right hand and the outer segment of the filiform between the thumb and the forefinger of the left hand, the tip of the filiform is inserted into the small aperture of the follower and this is helped to slip over until it is stopped at point B (fig 1) Catheterization may now proceed

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NEW PLASTIC DRAINAGE TUBING

A SMITH KINNE AND HAROLD W BRUSKEWITZ

From Sherman Hospital, Elgin, Ill

Everyone occasionally experiences difficulty with catheter drainage following bladder or prostatic surgery It is well established that irrigation, whether open or closed, is rarely necessary since it begets only more irrigation and invariably causes more bleeding Blood clots on the floor of the bladder allow a catheter to float above the clot and decant the supernatent urine The small stringy clot that often clogs the eyes or lumen of the catheter is all that needs to be dislodged Open irrigation is always a potential source of infection

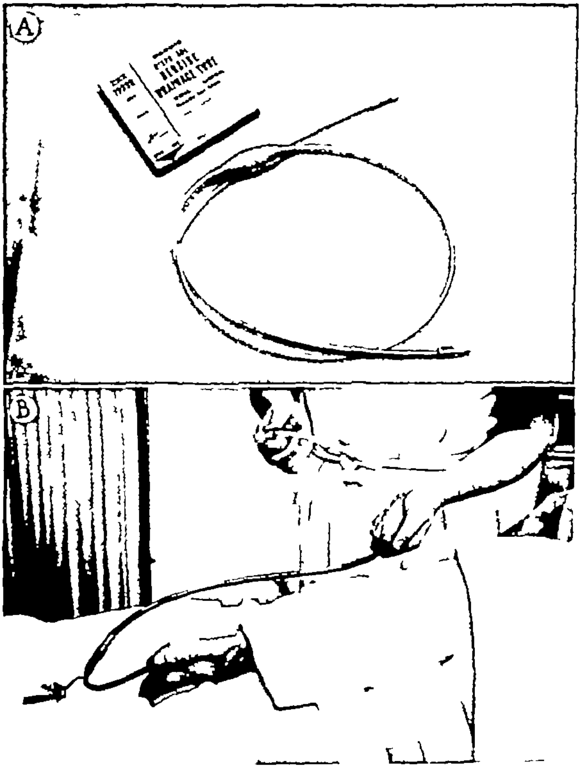

FIG 1

Since fluid is noncompressible, kinking the drainage tubing distally and milking or squeezing the tubing proximal to the kinking is usually successful in dislodging clots This avoids the necessity of any type of irrigation

The process of milking or pumping the drainage tubing worked satisfactorily with the old latex tubing, but with the advent of the newer large caliber plastic

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tubing this was no longer possible The new tubing has many advantages, namely, asepsis, disposability and larger caliber It became advantageous to devise a method of milking the tubing without having to disconnect it and resort to irrigation

With the co-operation of Mr E S Outwin of C R Bard, Inc , a plastic tubing has been devised with a plastic pump or bulb built into the drainage set (fig 1)

We have used this tubing in fifty or more cases of retropubic prostatectomy with success in every instance By merely kinking the tubing distal to the bulb and squeezing the bulb one can readily determine the patency of the catheter without disconnecting the tubing from the catheter (fig 1)

We wish to express our appreciation to Mr Outwin for his interest and cooperation in the production of this useful adjunct to prostatic surgery

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*Lowsley O S and Kirwin T J Clinical Urology Baltimore The Williams & Wilkins Company 1956 p 618

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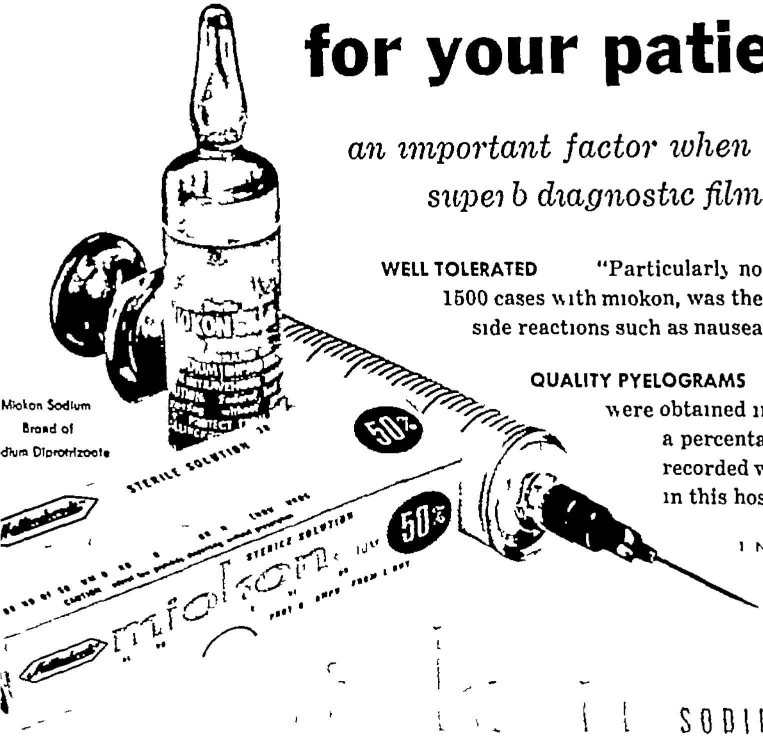

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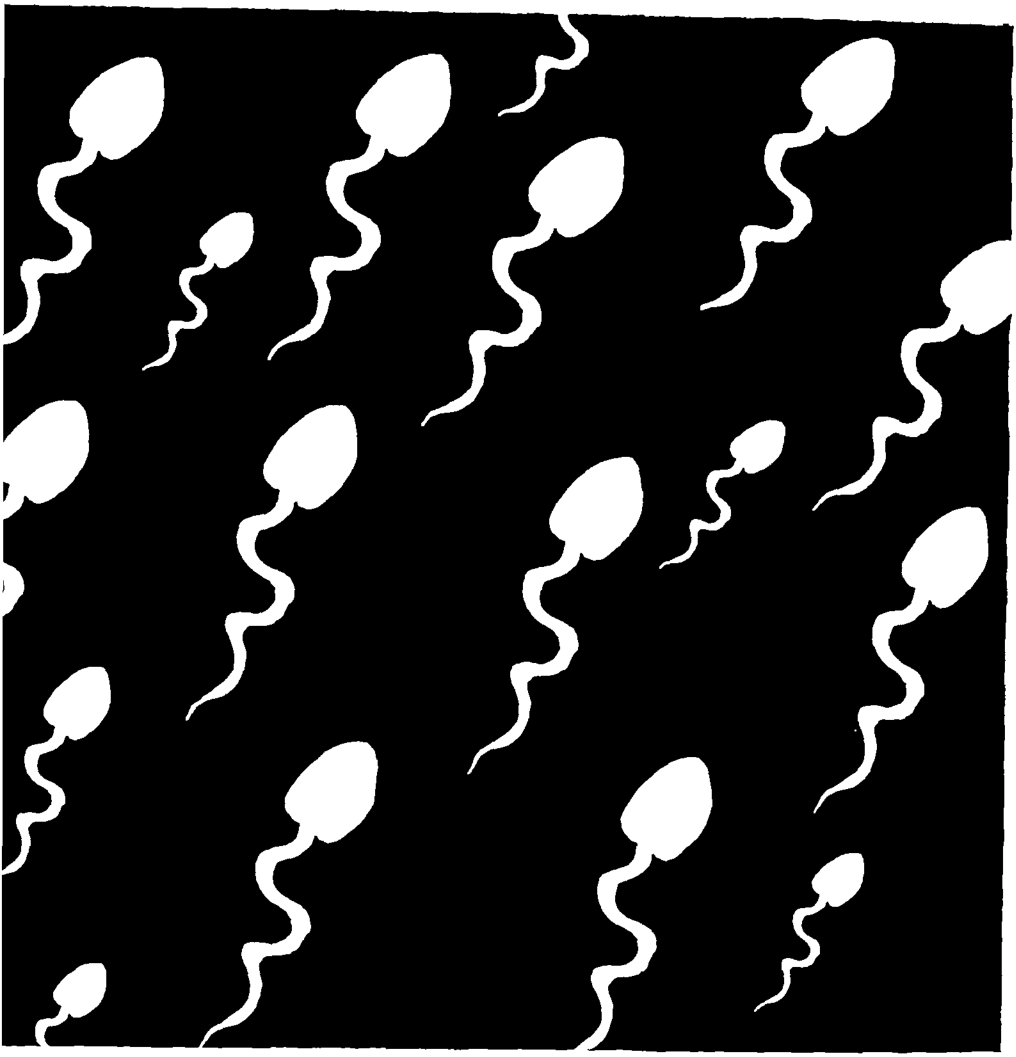

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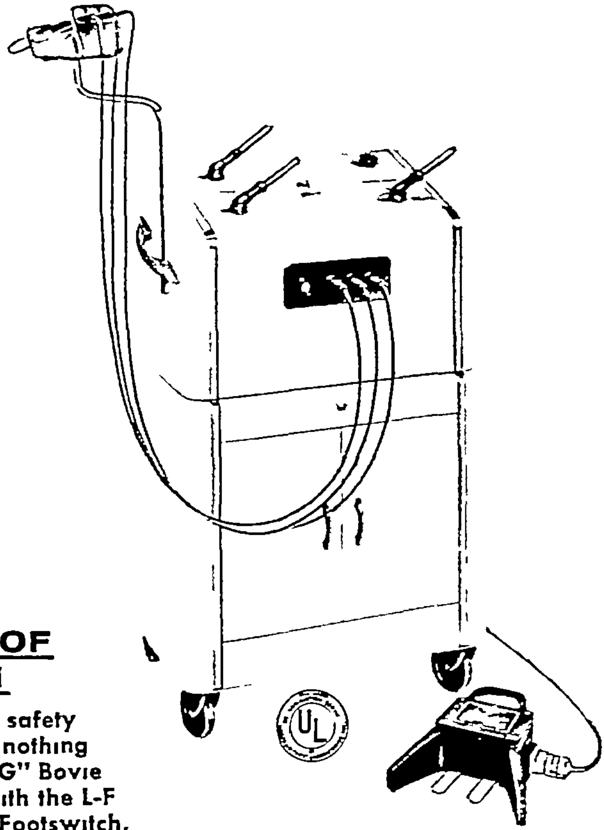

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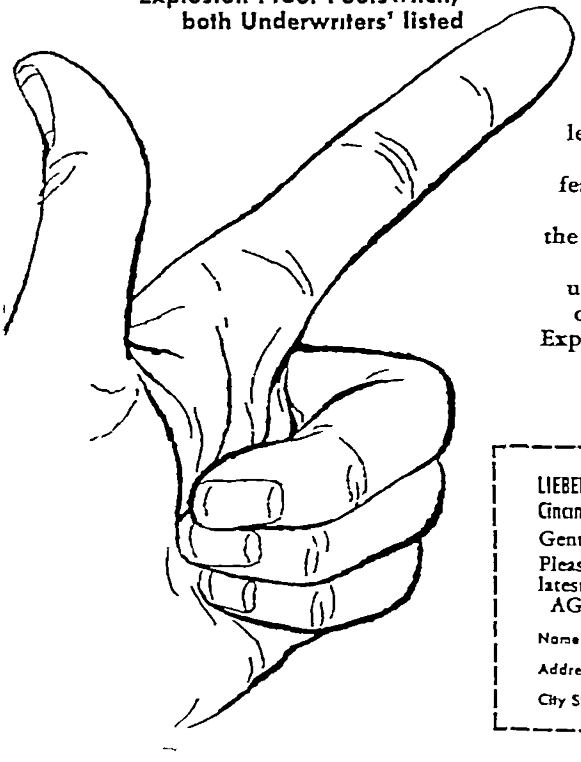

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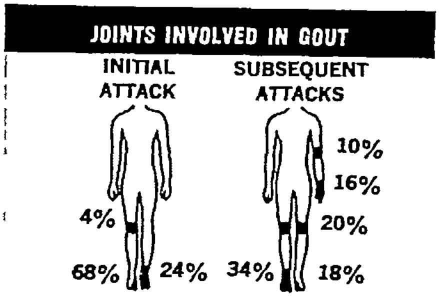

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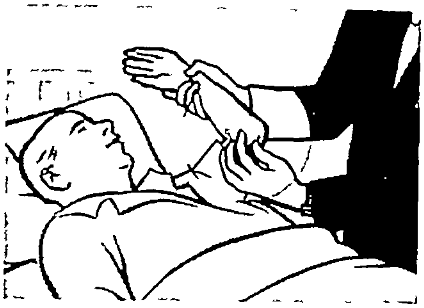

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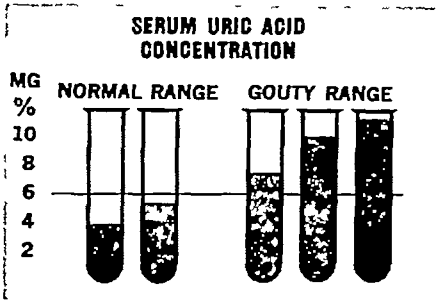

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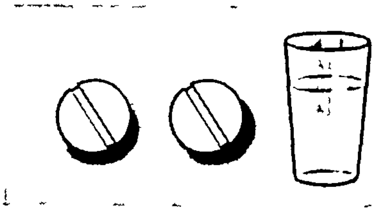

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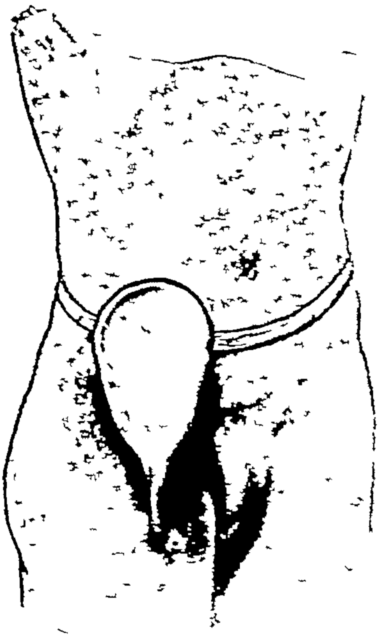

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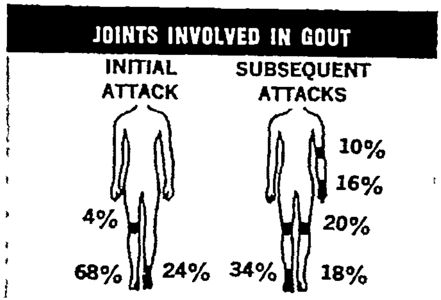
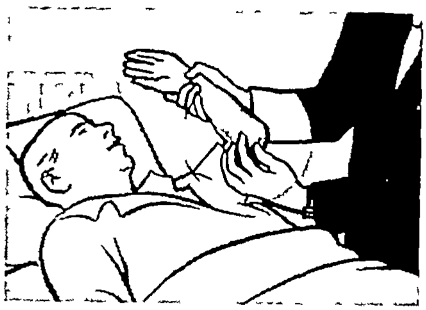
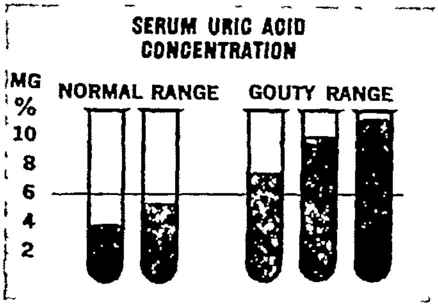


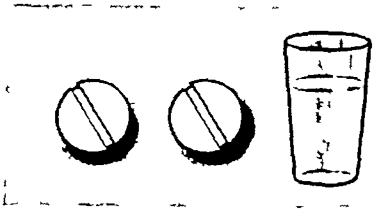
1. Recurrent joint pain followed by long periods of complete remission *(Percentages refer to incidence.)*



2. *Enlargement of bursae such as in this case involving the olecranon bursa.*



3. Elevated serum uric acid levels.



4. Colchicine test: full dose (0.5 mg.) every 1 to 2 hours until pain is relieved or nausea, vomiting or diarrhea occur. The test requires usually 8 to 16 doses. Pain relief is highly indicative of gout.

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Urinary excretion of uric acid is approximately doubled.
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Formation of new tophi can often be prevented.
Fewer attacks and severity is reduced.

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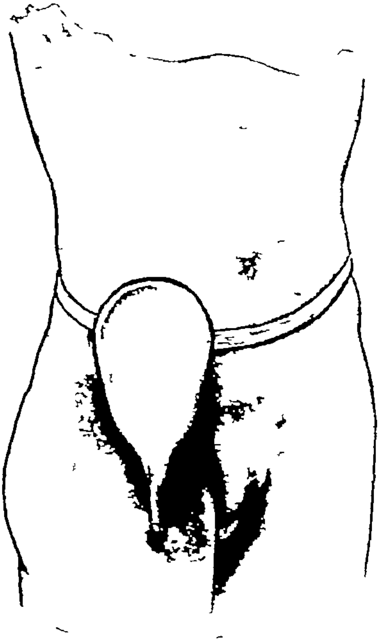

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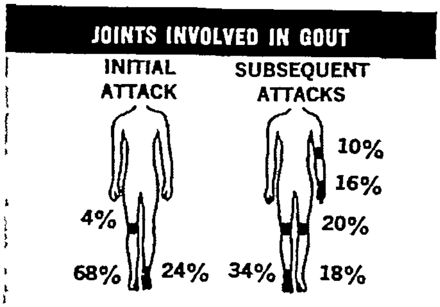

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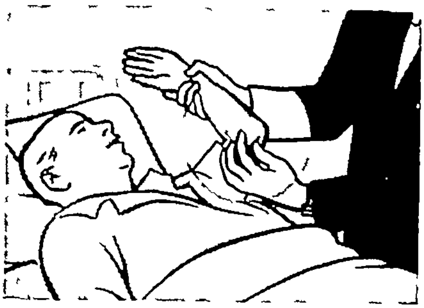

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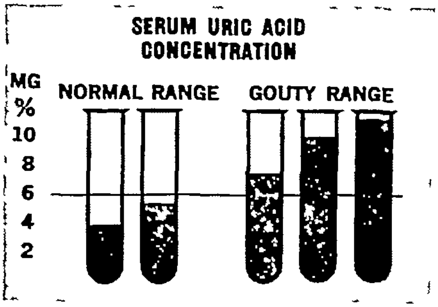

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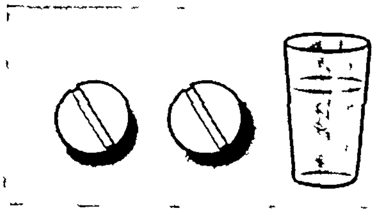

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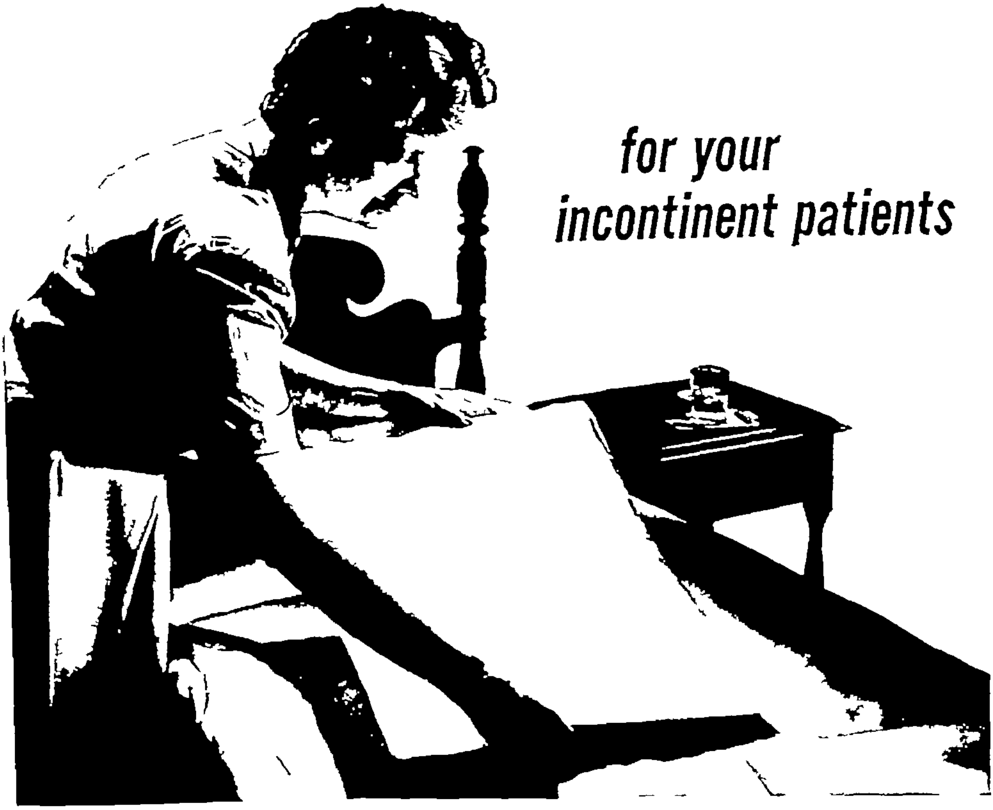

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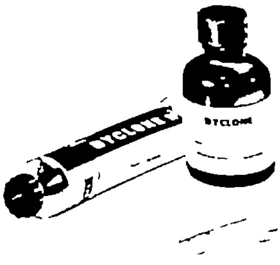

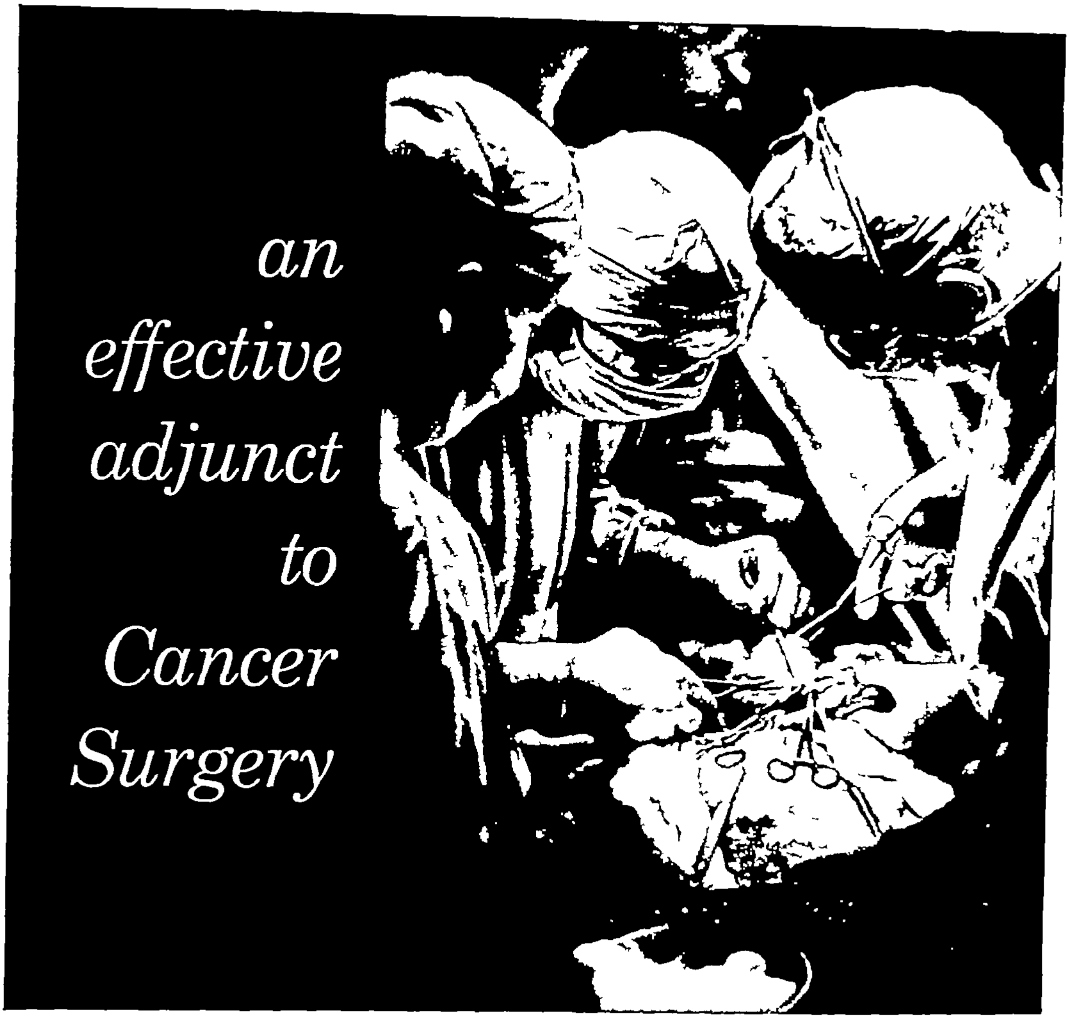

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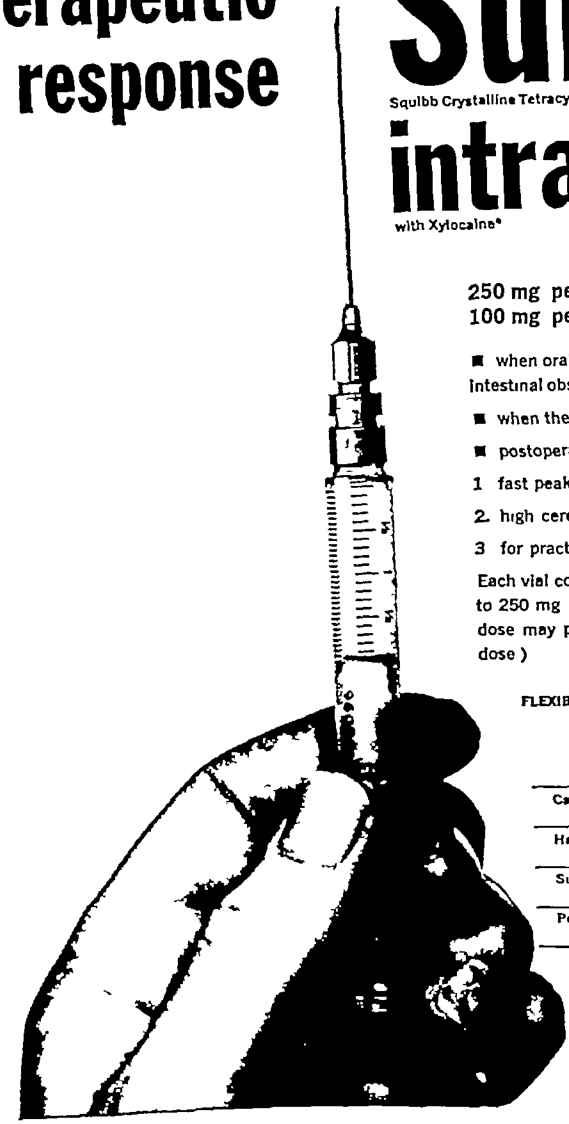

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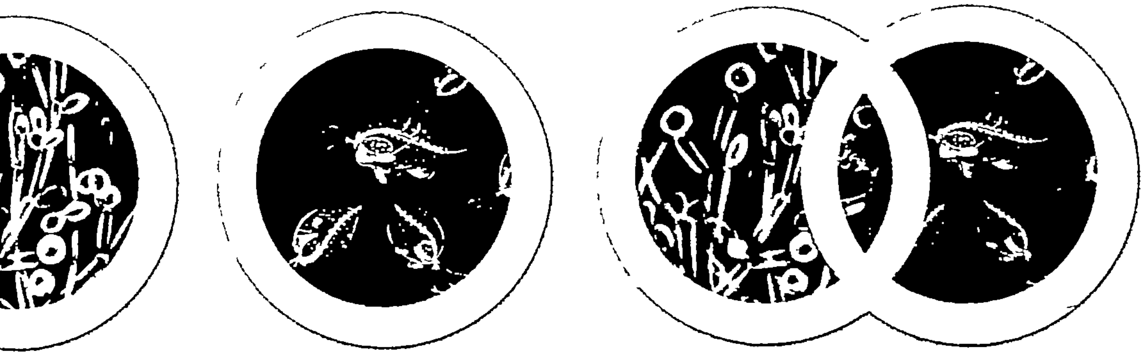

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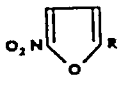

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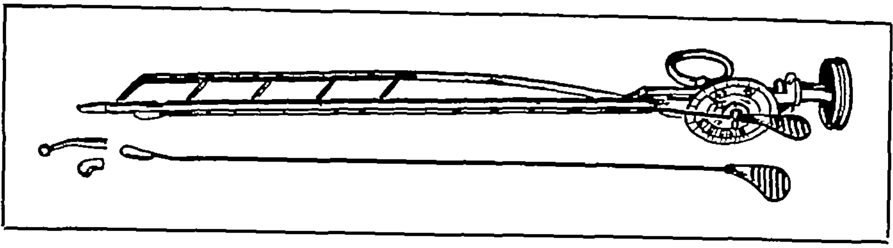

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- infants, especially prematures
- those on corticoids
- those who developed moniliasis on previous broad-spectrum therapy
- those on prolonged and/or high antibiotic dosage
- women—especially if pregnant or diabetic

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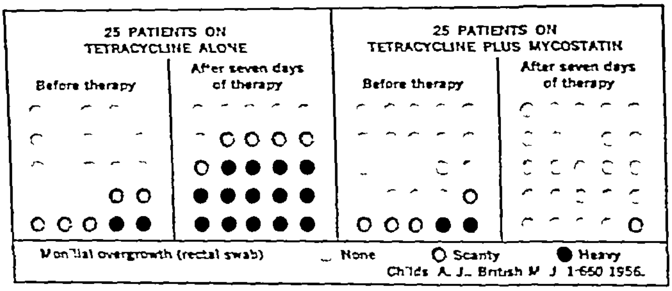

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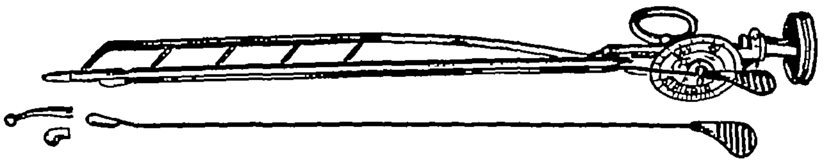

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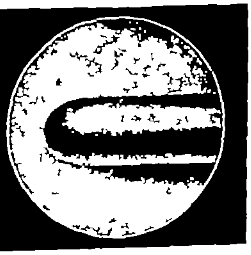

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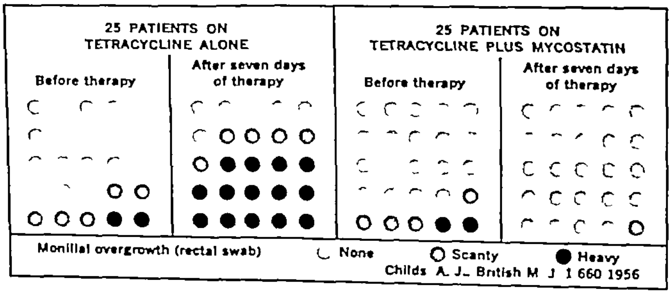

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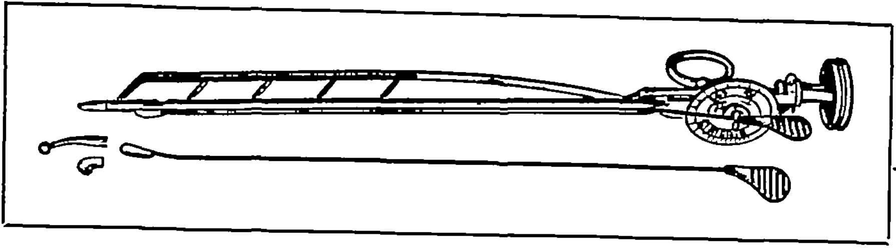

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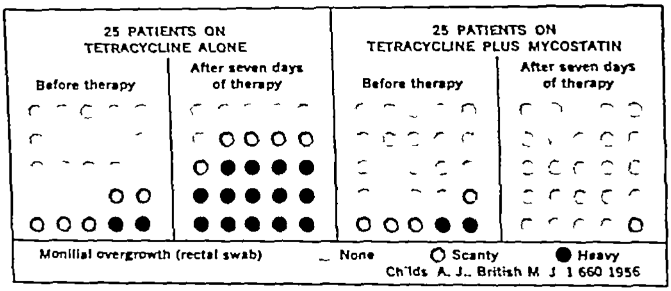

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Medical Management of Urinary Tract Infections, *The Medical Clinics of N A.*, Sept 1956 (Saunders)

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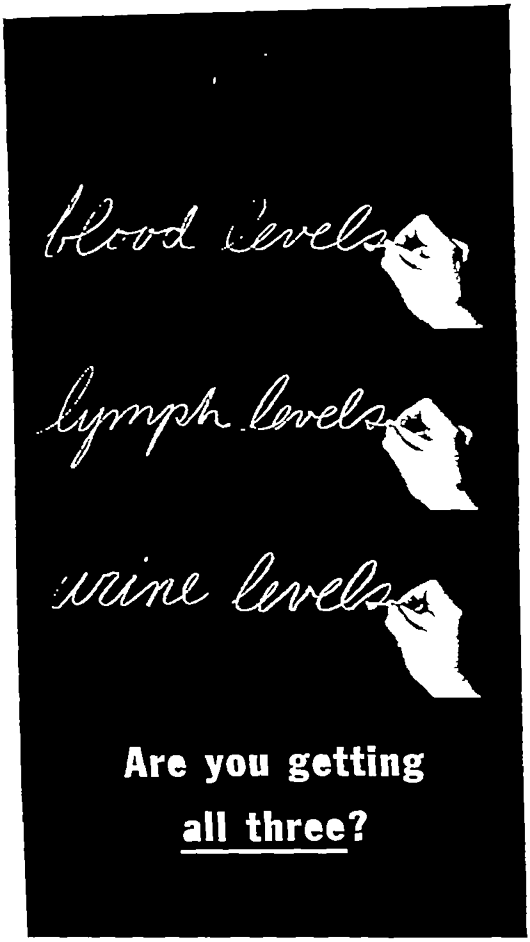

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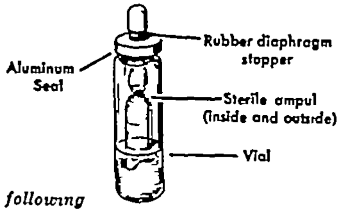

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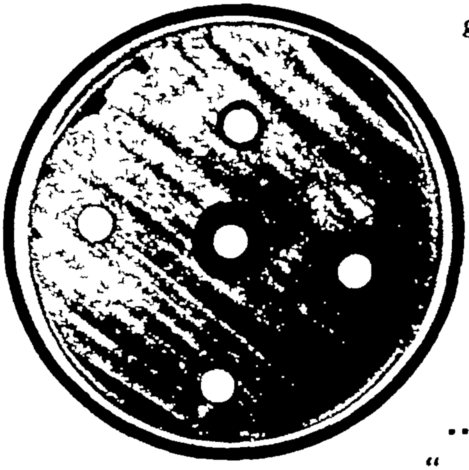

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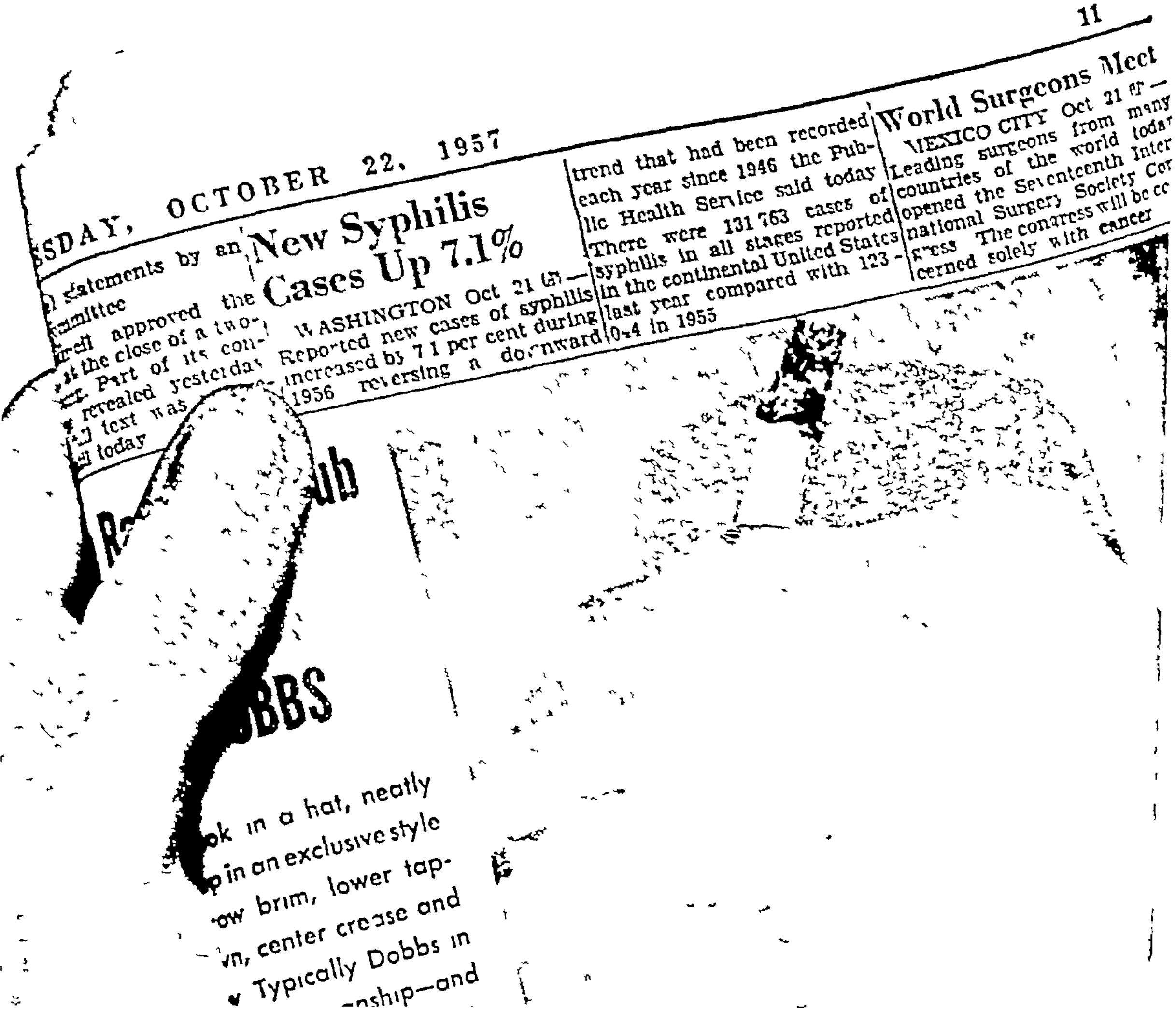

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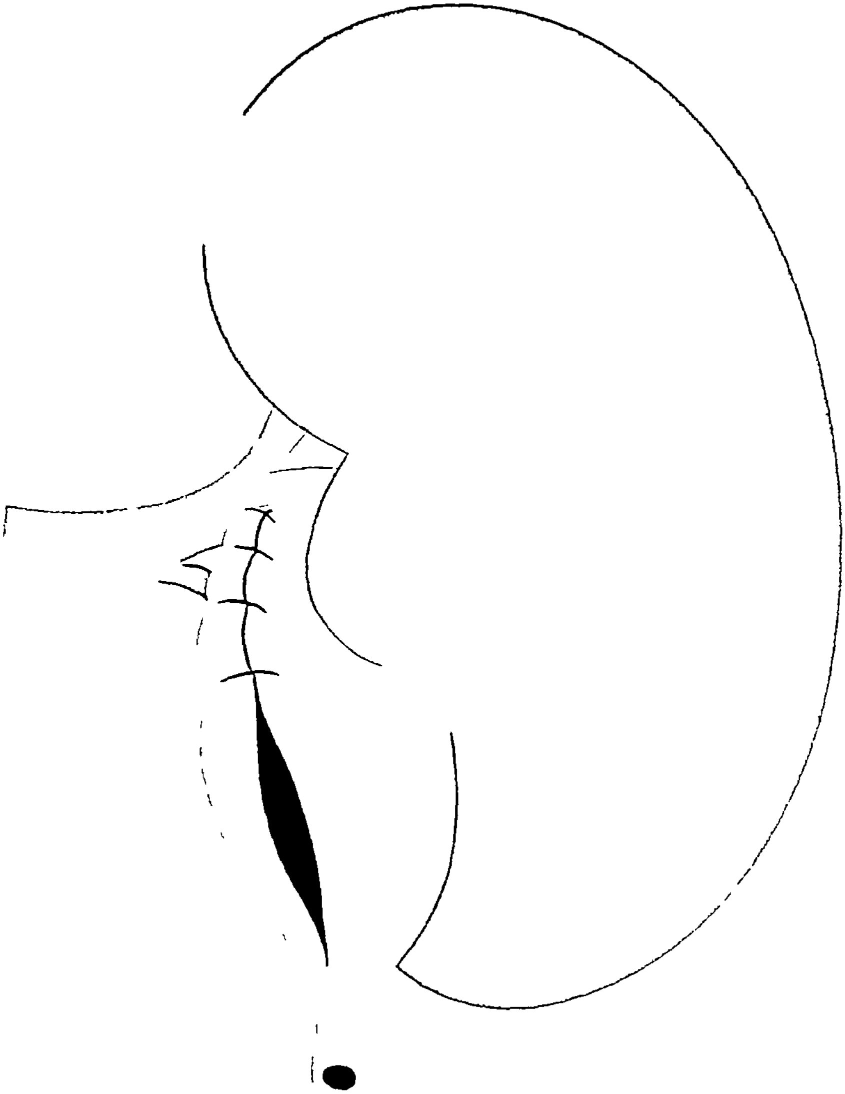

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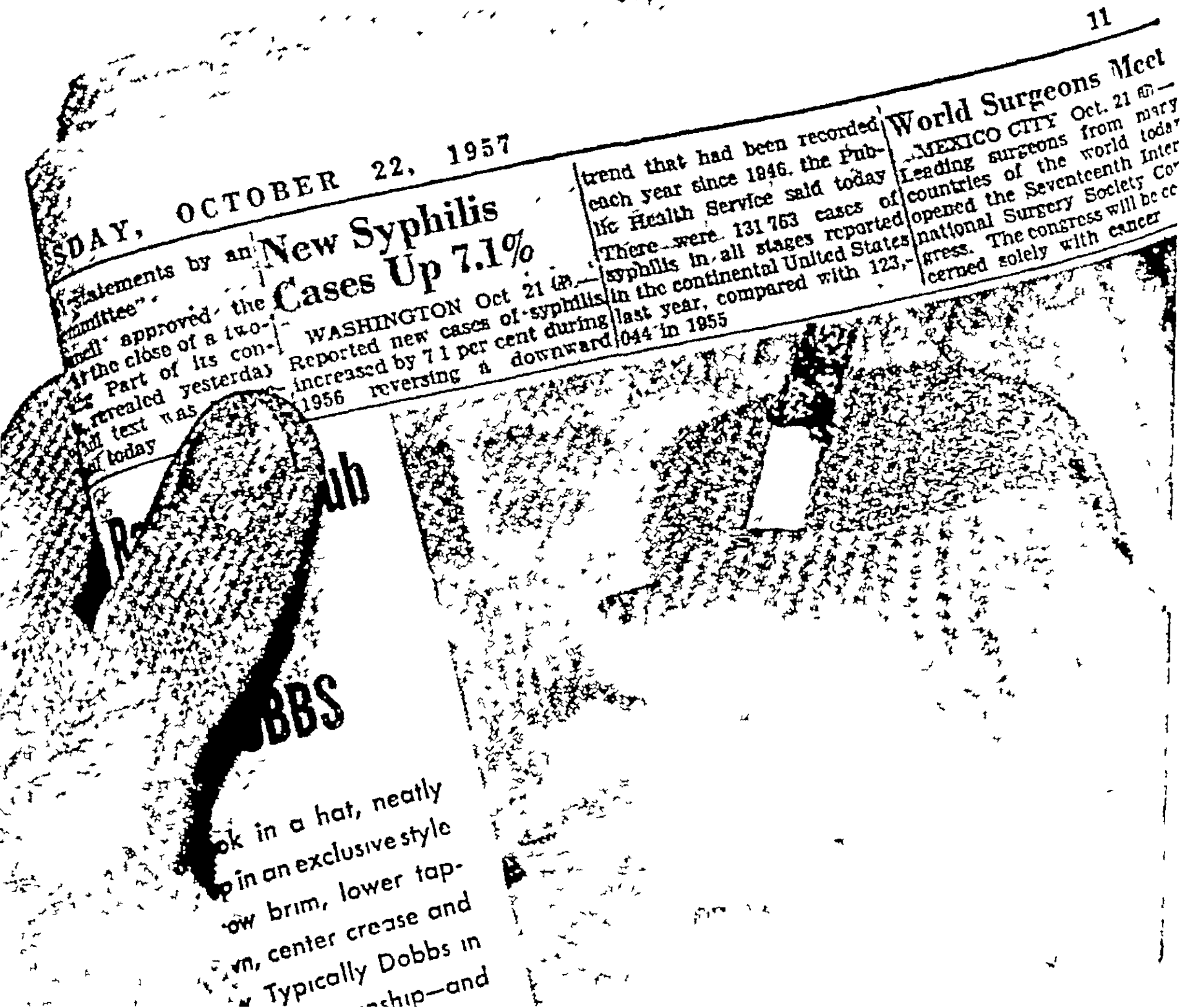

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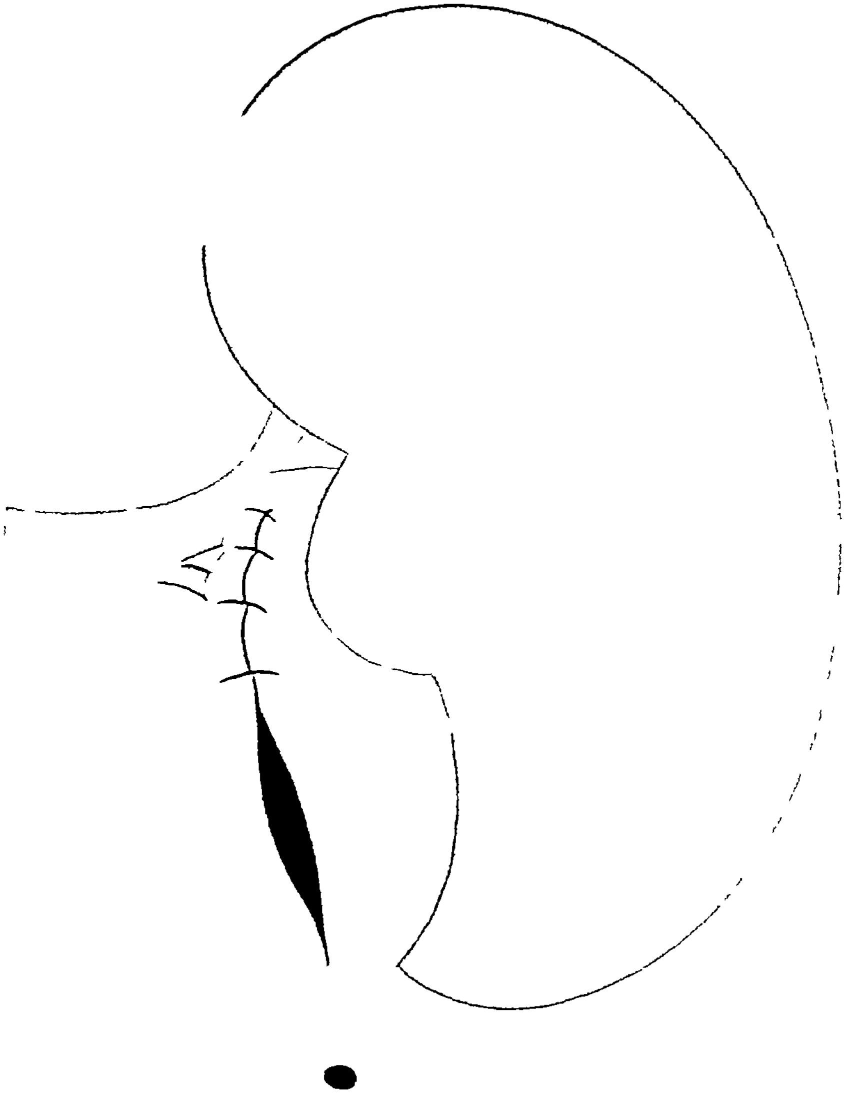
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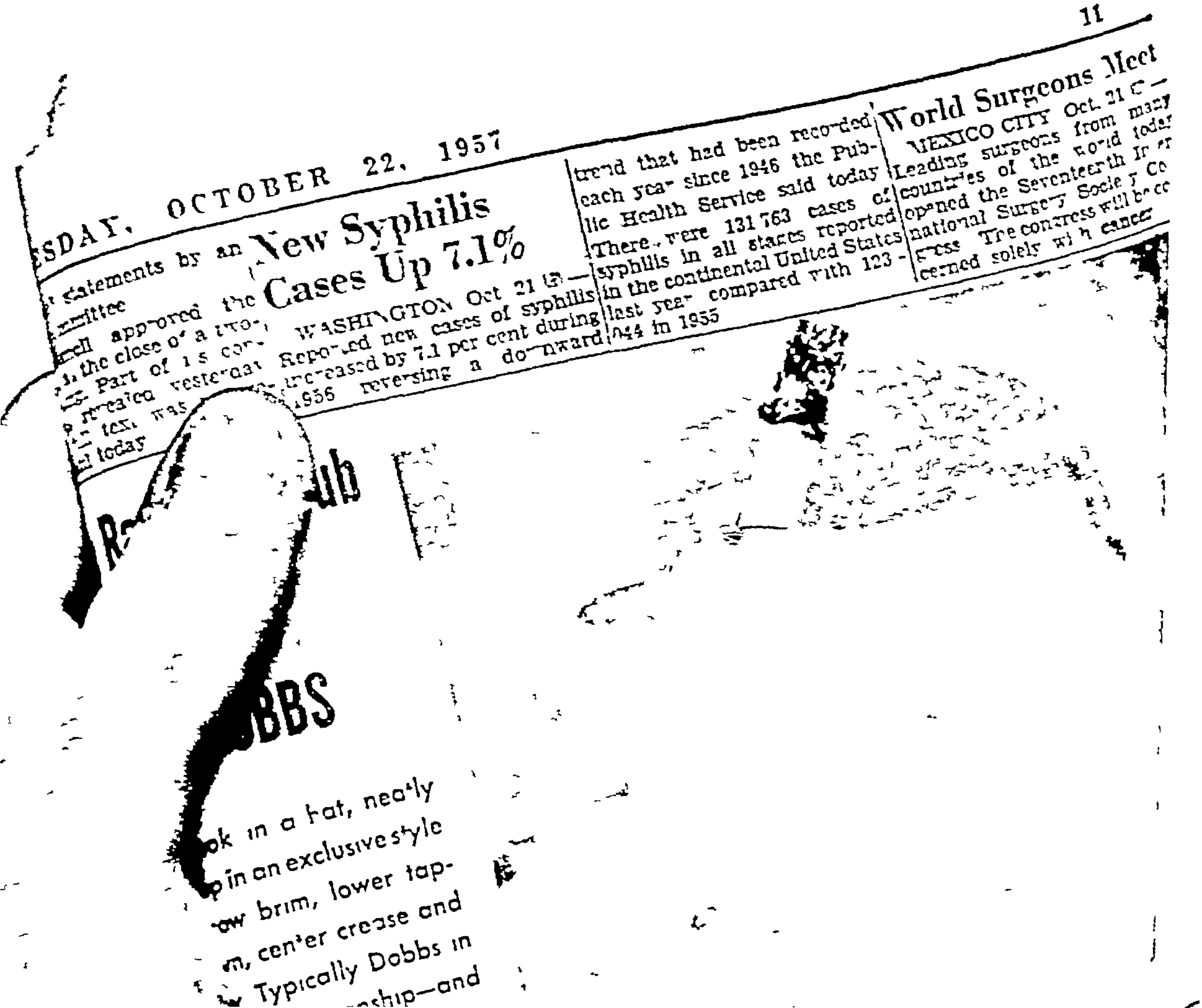

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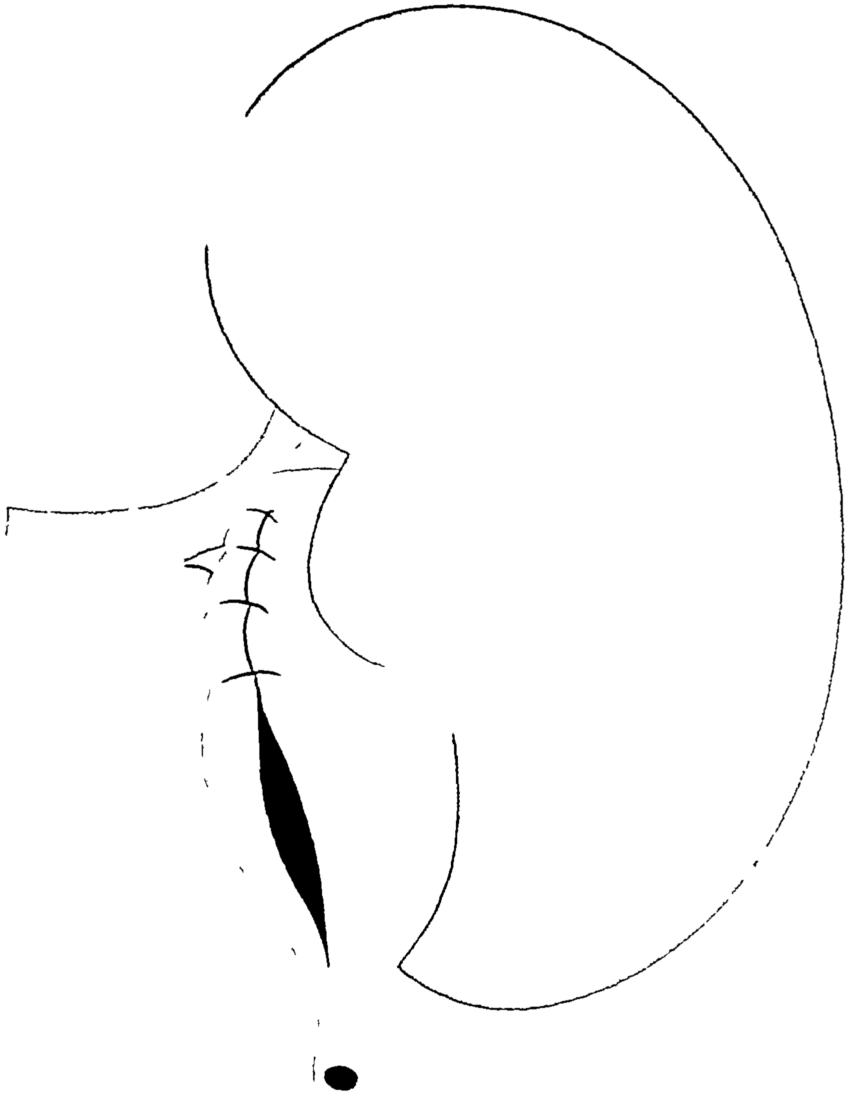

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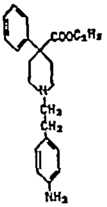

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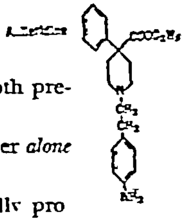

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INTRAVENOUS: Adults—50 to 100 mg added to 500 cc. of 5 per cent dextrose solution. Inject 5 to 10 mg slowly followed by the amount desired at a relatively slow drip

PRECAUTIONS The rare instances of respiratory depression sometimes seen with LERITINE and other potent narcotic analgesics can be readily reversed with the antagonist NALLINE (N Allylnormorphine) LERITINE may be habit forming Subject to the Federal Narcotic Law

SUPPLIED: *ORAL.* Tablets 'LERITINE anileridine 25 mg each (present as the dihydrochloride) bottles of 100 and 500

PARENTERAL LERITINE available as Injection LERITINE anileridine 25 mg /cc. (present as the phosphate) in boxes of 25 1-cc. and 25 2-cc. ampuls and in 30-cc. vials

1 Keesling R., Hinds E. C., and Keats A. S Principles of Drug Evaluations in Dental Surgery Antihistamines and Analgesics (Paper read at the Thirty fifth Gen. Meeting of the International Assoc. for Dental Research Atlantic City March 21 24 1957) 2. Orahovats, P D Lehman E. G Chapin, E. W Pharmacology of Ethyl 1-(4 Aminophenethyl)-4 Phenylisonipecotate Anileridine A New Potent Synthetic Analgesic Journal of Pharmacology and Experimental Therapeutics, Vol. 119 No 1 (January) 1957 3 Stage, J T. Anileridine as an Anesthetic Agent. Journal of the Florida Medical Association 44 143 145 (August) 1957 4 Keats, A. S., Telford J., Kurosu Y Studies of Analgesic Drugs Anileridine Dihydrochloride Anesthesiology 18 690-697 (September-October) 1957 5 Riffin I. M., Presing R., Wheaton H H., Landman M E., and Schwarz, B E. "A New Synthetic Analgesic, Anileridine," Scientific Exhibit, 106th A.M.A. Annual Meeting New York June 3 7 1957

Additional information is available to physicians on request.

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A new orally potent analgesic

'LERITINE'

ANILERIDINE

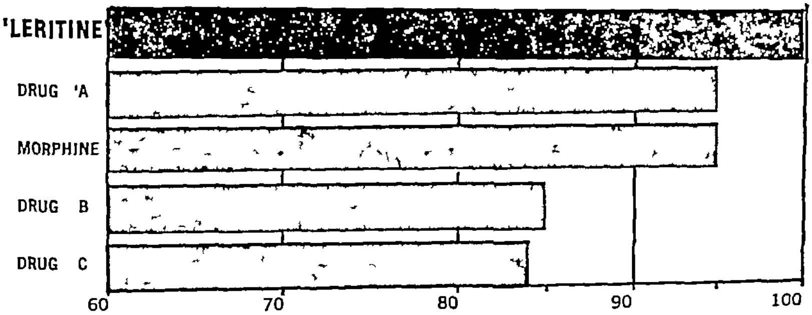
unsurpassed even for intense pain

WHAT INVESTIGATORS SAY

- In one series of 100 patients who received 60 mg of anileridine every 4 hours for a 24 hour period, 95% reported relief of pain [1]
- a potent analgesic with high oral activity and relatively mild side reactions It has a prompt onset of action and a long duration of analgesia. [2]
- In a series of 300 patients anileridine used as a primary anesthetic agent, appeared to be more potent than meperidine, and with the drip method no significant apnea or hypotension occurred Analgesia appeared to persist up to three hours postoperatively [3]
- In this study anileridine was found to be two and one half times as potent an analgesic as meperidine on a milligram basis [4]
- In a comparative study of 278 patients LERITINE' gave profound relief with potency approaching that of morphine with minimal side effects [5] This is illustrated in the following chart

CHART 1 COMPARATIVE RELIEF OF POSTOPERATIVE PAIN (3 Day Period)

Percentage of Adult Patients Experiencing Complete Pain Relief



Long acting LERITINE gave profound relief with fewer doses in this study of pain control in 278 patients after surgery The patients were observed during three post operative days to compare the analgesic potency of anileridine morphine sulfate and three other narcotic analgesics

Onset of relief was from 10 to 30 minutes after intramuscular injection of anileridine. Duration of relief varied from 2 8 hours No side reactions or toxic effects from anileridine were encountered

PLUS

Uromide Plus Tablets

for

INFECTION

combining **ANTIBACTERIAL ACTION** with Uromide

Each enteric coated Uromide Plus Tablet contains

Methenamine Mandelate	250 mg
Uromide (Salicylamide-Edwards)	250 mg

When combined therapy is indicated for.

INFECTION—Methenamine Mandelate's specific action on the urinary tract controls 75% of the common urinary infections . provides prolonged effectiveness with few resistant strains . is virtually free of untoward effects does not cause hypersensitization.

STONE FORMATION—is inhibited by Uromide The high glucuronide levels which inhibit stone formation create the desired environment for clearing up infection rapidly with Methenamine Mandelate.

PAIN RELIEF—Analgesia provided by Uromide further enhances the synergistic action of Uromide Plus Tablets

Dosage 2 tablets Q I D

Supplied Bottles of 100 and 500

a companion to Uromide Tablets . . Ne

Uromide Tablets

for

PREVENTION OF STONES

*in long range therapy "There was no appearance of new calculi in 17 of the 19 patients "**

The **ADVANTAGES** of **UROMIDE TABLETS** are

EXACT DAILY DOSAGE in just three tablets for a convenient with meals schedule.
ECONOMY—a major factor in long range therapy

"Salicylamide proved even better than acetylsalicylic acid and is used in all cases now All patients in this series had had a stone episode within a year of starting treatment or had renal calculi in situ at the time."*

Each Uromide Tablet contains 667 mg of salicylamide buffered with aluminum hydroxide.

Dosage one tablet T I D
Supplied Bottles of 100 and 500

*E L Prien and B S Walker

SO FUNDAMENTAL YOU KNOW IT WORKS

NEW PYRIDIUM® TRI-SULFA

PHENYLAZO-TRISULF PYRIM [illegible]

the obviously right combination of the original urinary tract analgesic and the classic triple sulfa for treatment of urinary tract infections

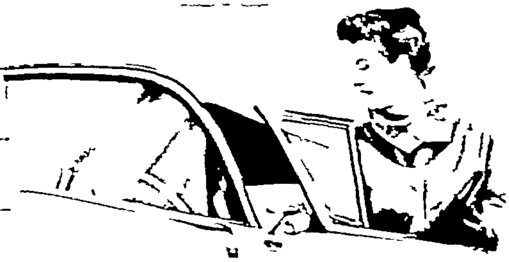
Relief of painful or uncomfortable symptoms quickly; prompt, efficient control of the infection, the only sulfa combination which provides Pyridium in the full therapeutic dose with only 1 tablet q.i.d.

Pyridium Tri-Sulfa provides the quick and specific local action of Pyridium for relief of pain, urgency, frequency and nocturia. The triple-sulfa component is a therapeutic standard with well-established advantages over single sulfonamides: broader, more efficient antimicrobial attack, increased solubility at normally acid levels of urine (pH 5.5 or less), practical elimination of certain side effects (irritation, hematuria), reduced sensitization probability, significantly higher, more prolonged sulfa concentrations at lower dosage.

WARNER-CHILCOTT / OVER 100 YEARS OF SERVICE TO THE MEDICAL PROFESSION

Pm

YOURS is to provide safe and rapid control of urinary tract infection. Gantrisin offers bacteriostasis where needed — with therapeutically effective lymph and urine levels as well as adequate blood levels



YOUR PATIENT'S is based on how quickly your treatment brings relief. The Azo component adds swift control of urinary tract pain and discomfort.

SUCCESS in the treatment of urinary tract infections —

Azo Gantrisin

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The taste says, Yes!

BICILLIN® ORAL SUSPENSION *STABLE! READY TO USE!*

Benzathine Penicillin G Wyeth (Dibenzylethylenediamine Dipenicillin G)

A Superior Oral Penicillin for Children

SUPPLIED *Cherry flavor*—300 000 units per 5 cc tsp bottles of 2 fl oz
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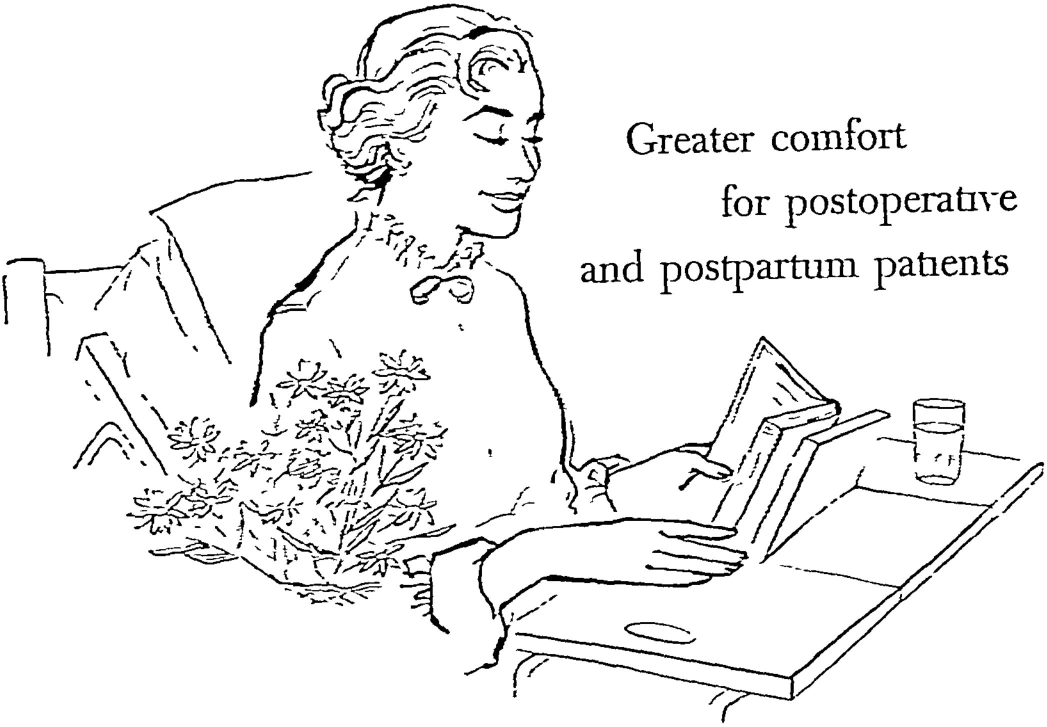

Greater comfort
for postoperative
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abdominal distention and urinary retention
can often be prevented or promptly relieved
—with less need for uncomfortable enemas and catheters

Urecholine®
Chloride
(Bethanechol Chloride)

'Urecholine' helps restore normal function after surgery and childbirth by increasing the muscular tone of the gastrointestinal and urinary tracts Postoperative "gas" pains can frequently be prevented or promptly relieved—with less need for uncomfortable enemas intubation, and suction apparatus Micturition is facilitated—without the discomfort and risk of infection inherent in catheterization

Administration and dosage. may be given prophylactically or therapeutically after surgery or childbirth. Usual oral dosage 10 to 30 mg. three or four times daily Usual subcutaneous dosage 5 mg. three or four times daily

Other indications. gastric atony and retention following vagotomy and other surgical procedures chronic functional urinary retention due to atony without obstruction megacolon, including congenital megacolon (Hirschsprung's disease) certain cases of paralytic ileus to counteract side effects of antihypertensive ganglionic blocking drugs

Supplied 5 mg. and 10 mg. tablets bottles of 100
1-cc. ampuls containing 5 mg.
'Urecholine' is a trademark of MERCK & CO., Inc.

MERCK SHARP & DOHME

REFER TO
PDR
PAGE 758

AZO GANTRISIN

Especially for urinary tract infections

Description Azo Gantrisin provides – in a single tablet – the wide spectrum, well tolerated antibacterial action of Gantrisin, the highly soluble, single sulfonamide, together with the local analgesic action of phenylazo-diamino-pyridine HCl

Properties Not only does Gantrisin provide high urinary concentrations with little likelihood of renal blocking, but therapeutic blood and lymph levels can readily be achieved and maintained Phenylazo-diamino-pyridine HCl is a local analgesic agent useful in urinary tract disorders, it generally provides rapid relief of dysuria, burning and frequency The orange-red dye appears promptly in the urine this often has a favorable psychologic effect

Indications Urinary tract infections when associated with pain or discomfort. Particularly useful in cystitis prostatitis and urethritis when due to susceptible organisms Also valuable before and after urologic surgery cystoscopy and catheterization

For dosage and supply refer to PDR page 758

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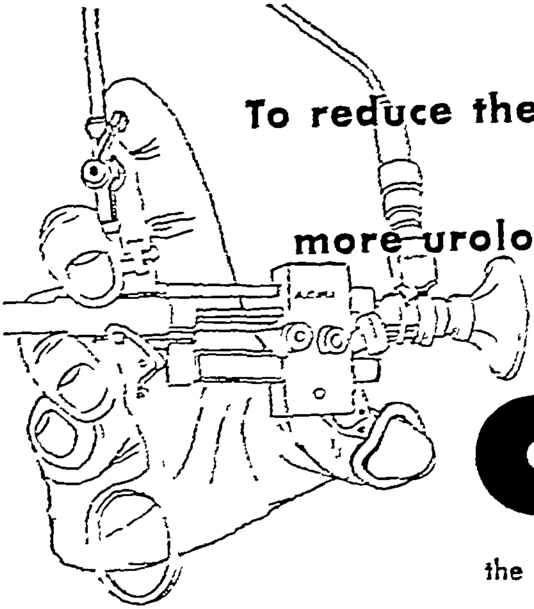
Comprehensive tetracycline-sulfonamide-

to



To reduce the risks in TUR surgery more urologists are changing to

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the nonhemolytic, isotonic irrigating fluid

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Cytal is safer

- surgical mortality is reduced—when isotonic irrigating solutions were used instead of distilled water in 2492 consecutive transurethral prostatic resections, only 0.96% mortality was reported.[1]
- hemolysis during resection is prevented
- hard clots are not formed on prostatic bed—venous ooze readily washes away
- operating time is shortened—loop need not be removed from instrument to clean off clotted blood.
- free of amino acids or nitrogen which can metabolize into toxic ammonia.

Cytal is more convenient

- optical qualities are excellent— "Cytal was selected from a choice of 30 nonhemolytic solutions because of its optical superiority when viewed through the lens of the resectoscope."[2]
- postoperative irrigation is required less frequently than when saline is used
- tendency of blood to form free clots or fibrin masses in the bladder is reduced.
- irrigation catheter does not become obstructed by clots

CYTAL* is available in sterile, pyrogen-free 1 liter Saftiflasks®
ready for immediate dilution and use

*A concentrated solution of [illegible]

1. Creevy, C. D., Surgery 23: 180, 1955
2. Schulte, P. L., Hammer, H. J., and Reynolds, L. R., J. Urology 71: 6[illegible], 1954

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new, lifesaving Furadantin®

brand of nitrofurantoin

intravenous solution for severe infections

A WIDE RANGE OF CLINICAL USEFULNESS .

in systemic infections such as septicemia (bacteremia), peritonitis, and other bacterial infections as of postoperative wounds and abscesses *In severe genitourinary tract infections* when the patient is unable to take FURADANTIN per os

... AND A WIDE RANGE OF BACTERICIDAL EFFECTIVENESS ...

wide-spectrum activity against most common pathogens • clinically effective against many antibiotic- or sulfonamide-resistant genera such as Aerobacter, Staphylococcus, Proteus, and certain strains of Pseudomonas.

... WITH CERTAIN UNIQUE ADVANTAGES

• negligible development of bacterial resistance • no reports of renal, hematopoietic or hepatic toxicity • no monilial superinfection • safe for continuous use without danger of thrombophlebitis

Full dosage instructions and discussion of indications and side effects are enclosed in each package. FURADANTIN *Intravenous Solution* is available to all hospital pharmacies

NITROFURANS—a *new* class of antimicrobials— neither antibiotics nor sulfonamides

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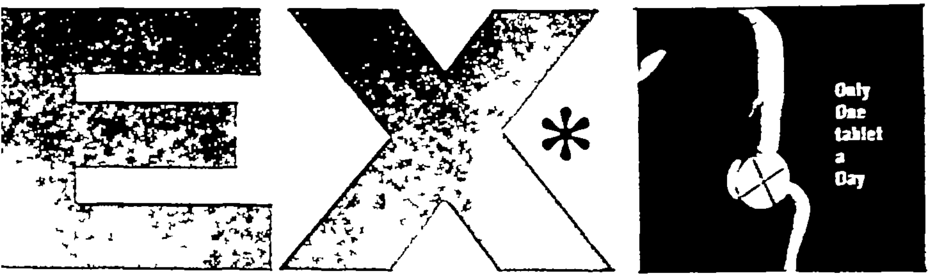
Unusual Antibacterial and Anti-infective Properties. More rapid absorption ... higher and better sustained plasma concentrations ... more soluble in acid urine than other sulfonamides ... freedom from crystalluria and absence of significant accumulation of drug even in patients with azotemia.[1]

Unprecedented Low Dosage. Less sulfa for the kidney to cope with ... yet fully effective. A single daily dose of 0.5 to 1.0 Gm. (1 to 2 tablets) maintains higher plasma levels than 4 to 6 Gm. daily of other sulfonamides—a notable asset in prolonged therapy.[2]

New Control Over Sulfonamide-sensitive Organisms. KYNEX maintains the prolonged high tissue concentrations of primary importance in treatment of urinary infections ... a therapeutic asset toward preventing manifest pyelonephritis as a complication of persistent bacteriuria during pregnancy and puerperium. Maintenance of sterile urine in such patients was accomplished with 1 tablet of KYNEX daily.[3]


EX*
Only One tablet a Day

Sulfamethoxypyridazine Lederle

Dosage The recommended adult dose is 1 Gm. (2 tablets) the first day followed by 0.5 Gm. (1 tablet) every day thereafter, or 1 Gm. every other day for mild to moderate infections. In severe infections where prompt, high blood levels are indicated, the initial dose should be 2 Gm. followed by 0.5 Gm. every 24 hours. Dosage in children according to weight, i.e., a 40 lb. child should receive 1/4 of the adult dosage. It is recommended that these dosages not be exceeded.

KYNEX—WHEREVER SULFA THERAPY IS INDICATED

Tablets Each tablet contains 0.5 Gm. (7½ grains) of sulfamethoxypyridazine. Bottles of 24 and 100 tablets.

Syrup Each teaspoonful (5 cc.) of caramel flavored syrup contains 250 mg. of sulfamethoxypyridazine. Bottle of 4 fl. oz.

References: 1. Grieble, H. G. and Jackson, G. G.: Prolonged Treatment of Urinary Tract Infections with Sulfamethoxypyridazine, *New England J. Med.* 258:1-7, 1958. 2. Editorial, *New England J. Med.* 258:[illegible], 1958. 3. Jones, W. F., Jr. and Finland, M.: Sulfamethoxypyridazine and Sulfachlorpyridazine, *Ann. New York Acad. Sc.* 69:[illegible], 1957.

*Reg. U. S. Pat. Off.

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Low
Dosage
KYN
for
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Infections

PYRIDIUM® RELIEVES PAIN PROMPTLY

[illegible]

fills the gap between complaint and correction of urinary tract disorders. In 20-25 minutes, Pyridium gives relief of urinary tract symptoms, even before the cause can be effectively treated. Diagnosis, antibacterial action or surgery may take time—but pain relief can be immediate with Pyridium, the standard urinary tract analgesic. **WARNER-CHILCOTT**

NEW!

PYRIDIUM®
TRI-SULFA
(phenylazo- [illegible])

controls infection
relieves pain promptly
with only 1 tab q i d

Specifically Recommended in the Treatment of Prostatic Carcinoma

"ESTRADURIN"®

Brand of polyestradiol phosphate

Long-acting Estrogen with Unique Mode of Action

- simulates physiologic release of estrogen
- acts as a synthetic gland secreting natural estrogen
- maintains constant effective levels

"Estradurin" offers a safe, efficient, simple, and reliable means of insuring constant effective estrogen levels in patients with prostatic carcinoma [1,2]

The unique mode of action is explained as follows [3,4]

No depot effect at site of injection — Within 24 hours, 90 per cent of the total dose disappears from the injection site. Clearance from the blood stream is also rapid, and within 48 hours varying amounts appear in the reticuloendothelial cells where storage is apparently passive.

Hydrolysis in the blood stream — As the amount of circulating polyestradiol phosphate falls below a certain level, more passes from the reticuloendothelial system into the blood stream Biologically active units of estradiol are slowly split off from the parent molecule The free estradiol then exerts a normal estrogenic influence and is metabolized by the body in the same manner as the endogenous hormone.

Suggested Dosage 40 mg intramuscularly every two to four weeks or less frequently, depending on the clinical response of the patient If the response is not satisfactory, doses up to 80 mg may be used Increasing the dose primarily prolongs the duration of action, but the amount of estrogen available at any one time is not significantly increased

Availability No 451 — Each package provides One "Secule"® containing 40 mg polyestradiol phosphate and one 2 cc ampul of sterile diluent.

Bibliography and literature on request

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PYRIDIUM® RELIEVES PAIN PROMPTLY

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fills the gap between complaint and correction of urinary tract disorders. In 20-25 minutes, Pyridium gives relief of urinary tract symptoms, even before the cause can be effectively treated. Diagnosis, antibacterial action or surgery may take time—but pain relief can be immediate with Pyridium, the standard urinary tract analgesic. **WARNER-CHILCOTT**

NEW!

PYRIDIUM®

TRI-SULFA

[illegible]

controls infection
relieves pain promptly
with only 1 tab q i d

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- MODERATE COST

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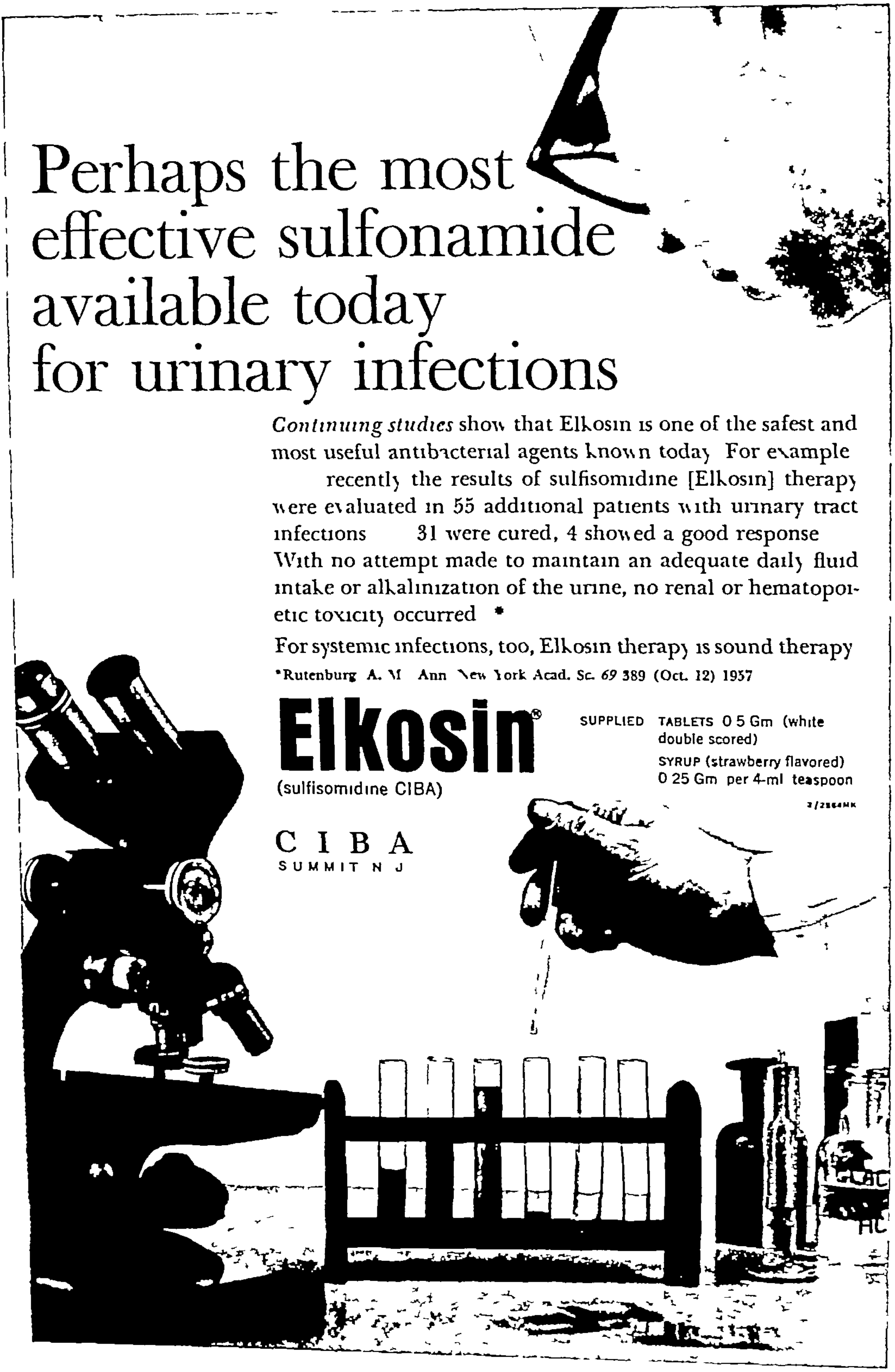

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Continuing studies show that Elkosin is one of the safest and most useful antibacterial agents known today For example recently the results of sulfisomidine [Elkosin] therapy were evaluated in 55 additional patients with urinary tract infections 31 were cured, 4 showed a good response With no attempt made to maintain an adequate daily fluid intake or alkalinization of the urine, no renal or hematopoietic toxicity occurred *

For systemic infections, too, Elkosin therapy is sound therapy

*Rutenburg A. M Ann New York Acad. Sc. *69* 389 (Oct. 12) 1957

Elkosin®
(sulfisomidine CIBA)

SUPPLIED TABLETS 0 5 Gm (white double scored)
SYRUP (strawberry flavored) 0 25 Gm per 4-ml teaspoon

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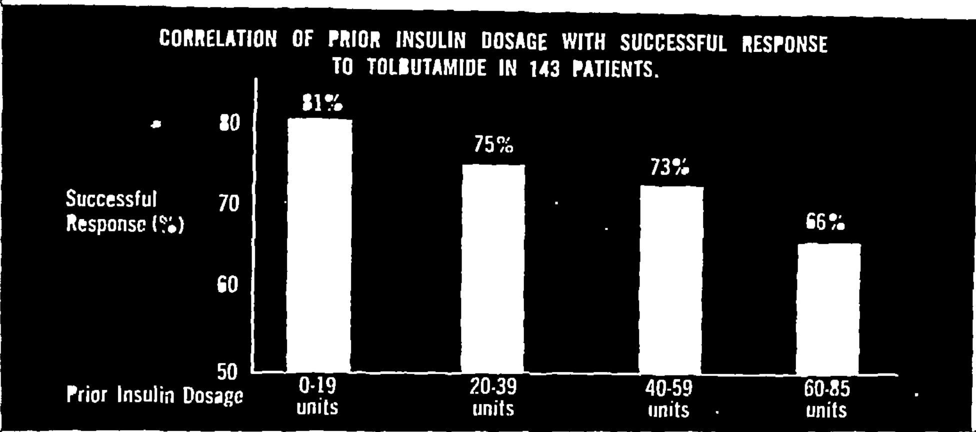
CLINICAL BRIEFS FOR MODERN PRACTICE



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can selected diabetics on insulin be changed over to tolbutamide on an ambulatory or outpatient basis?

Yes By gradually reducing insulin dosage during the change-over and by frequent daily testing of the urine—by the patient—for sugar and ketone bodies

Source—Sugar, S J N Ann New York Acad Sc *71* 256 (July 10) 1957

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the STANDARDIZED urine-sugar test for reliable quantitative estimations
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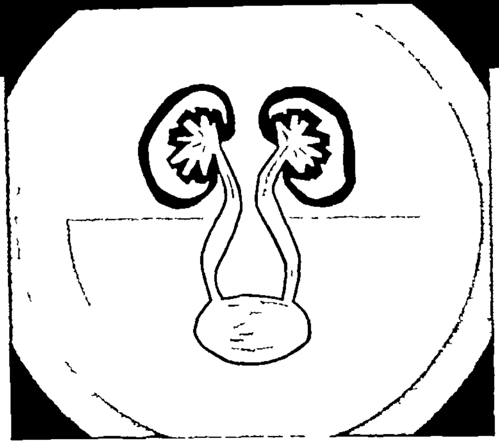
NOW a bactericidal urinary antiseptic

CATHOZOLE®

(Sodium Novobiocin with Sulfamethylthiadiazole)



Antibacterial spectrum 'CATHOZOLE' is bactericidal and has an exceptionally broad antibacterial spectrum It is highly effective against the most frequent and even against some of the most stubborn urinary tract infections (*E coli P vulgaris* pseudomonas and staphylococcus)

Speed of action Pain, frequency, burning and irritation usually subside within 24 hours

Urinary tract concentration Achieves effective levels, higher than those attained with any other urinary tract antiseptic

Solubility *Highest* solubility and *lowest* acetylation of any available urinary tract antiseptic Less hazard of crystalluria

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help normalize prothrombin time before surgery

"has a more prompt, more potent and more prolonged effect than the vitamin K analogues"*

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VITAMIN K_1

Reduce the hazard of hemorrhage due to hypoprothrombinemia during or after surgery tonsillectomy obstetrical and gynecological procedures, surgery of the newborn (especially prematures) neurosurgery, thoracic surgery, intestinal surgery, biliary tract surgery, rhinoplasty, surgery in any highly vascular area.

Especially indicated in patients with obstructive jaundice or when prothrombin level is depressed following administration of anticoagulants barbiturates salicylates, antibiotics sulfonamides or phenylbutazone Can also be used postoperatively to combat hemorrhage due to hypoprothrombinemia

Dosage Surgery—up to 50 mg orally at least 24 hours preoperatively or up to 50 mg intravenously at least 12 hours preoperatively to restore prothrombin to safer levels

Supplied Tablets 5 mg bottles of 100 Emulsion each 1-cc ampul contains 50 mg boxes of 6 ampuls

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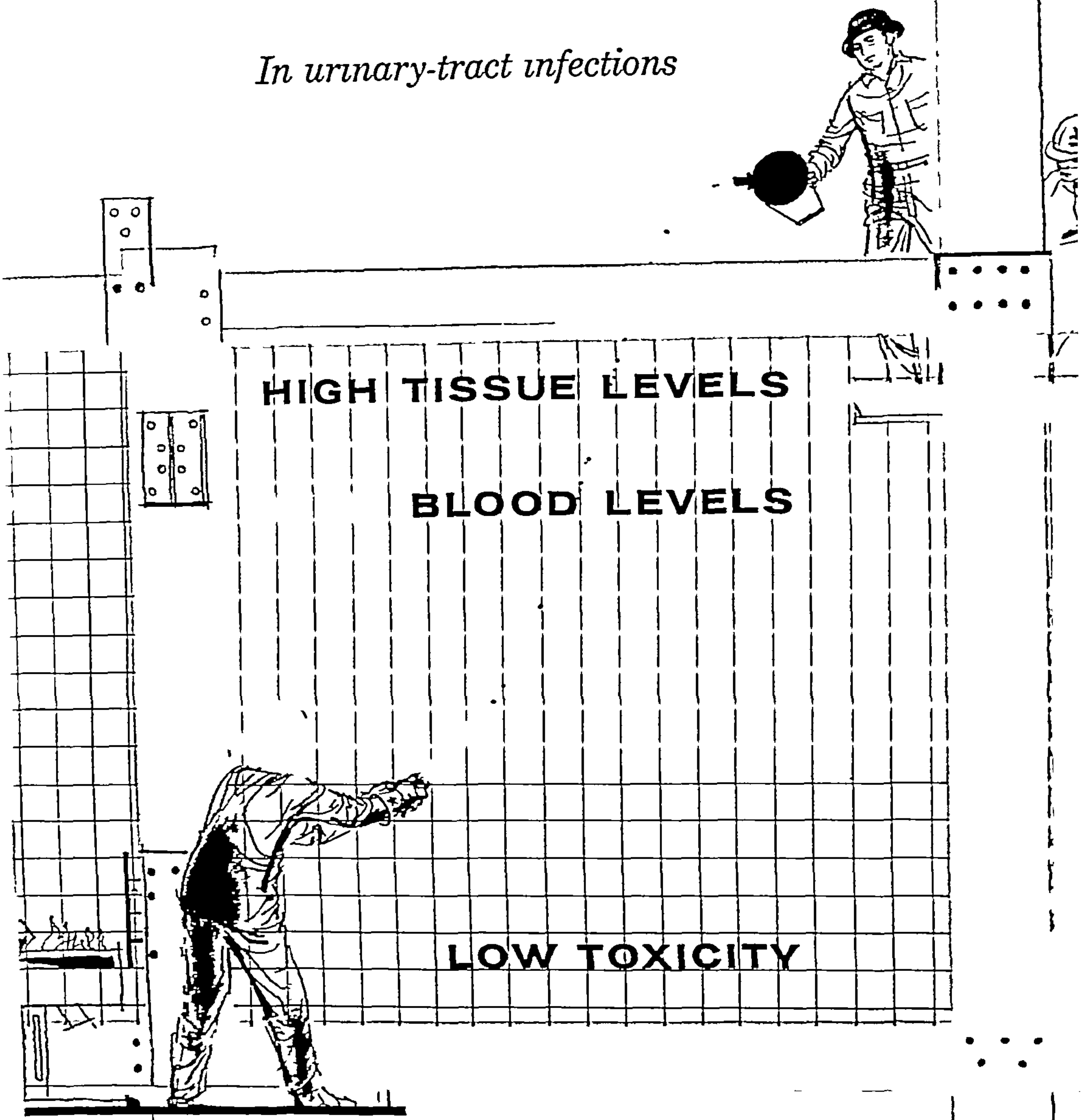
Council on Pharmacy and Chemistry New and Nonofficial Remedies, Philadelphia, J B Lippincott Co 1956 p 505

In urinary-tract infections



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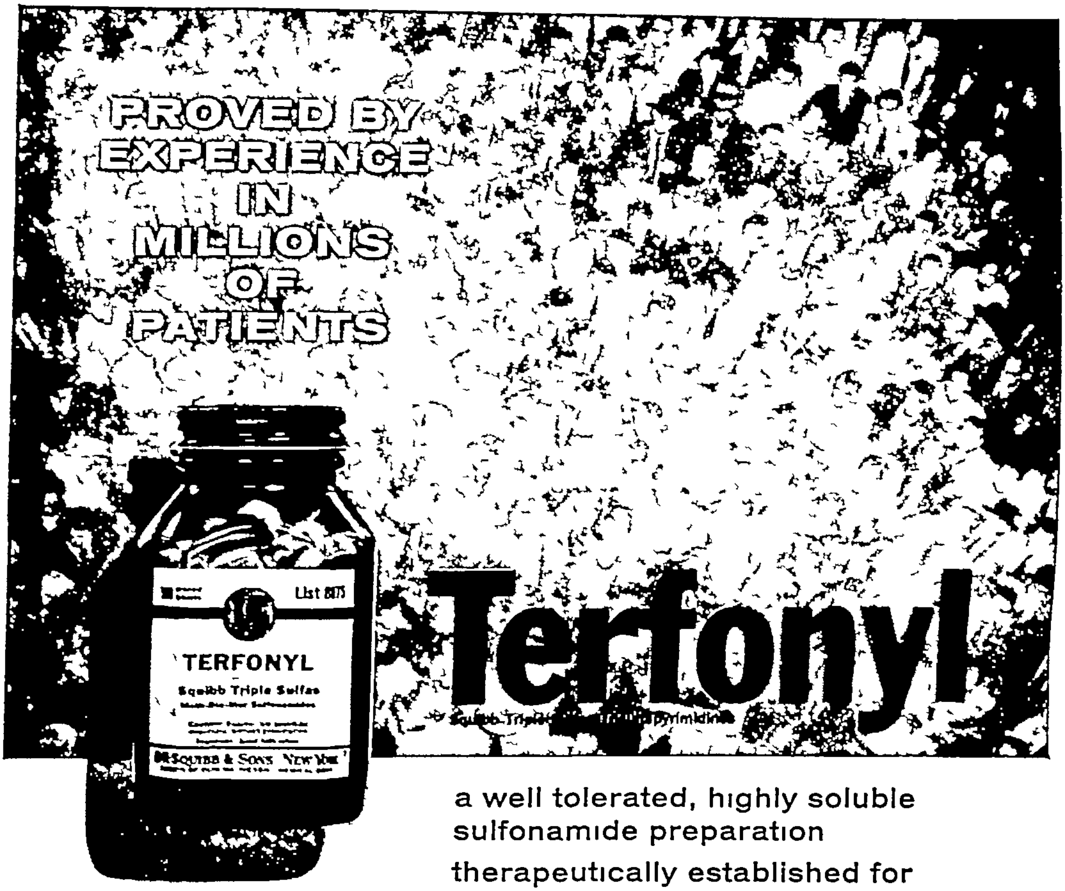

a well tolerated, highly soluble sulfonamide preparation

therapeutically established for your clinical use

For many urinary, respiratory and other bacterial infections

you'll find Terfonyl a drug of choice because of its high degree of efficacy maximum safety and wide patient acceptability To date, physicians have prescribed Terfonyl for millions of patients with excellent results.

Advantages of Terfonyl

- clinically proved in millions of patients
- provides effective sulfonamide therapy with minimal risk
- highly soluble at the pH range of the kidneys
- wide antibacterial spectrum—including gram positive and gram negative organisms
- produces rapid high blood levels
- economical

Supply

Tablets 0 5 Gm bottles of 100 and 1000 Raspberry flavored Suspension 0 5 Gm. per teaspoonful (5 cc.) pint bottles

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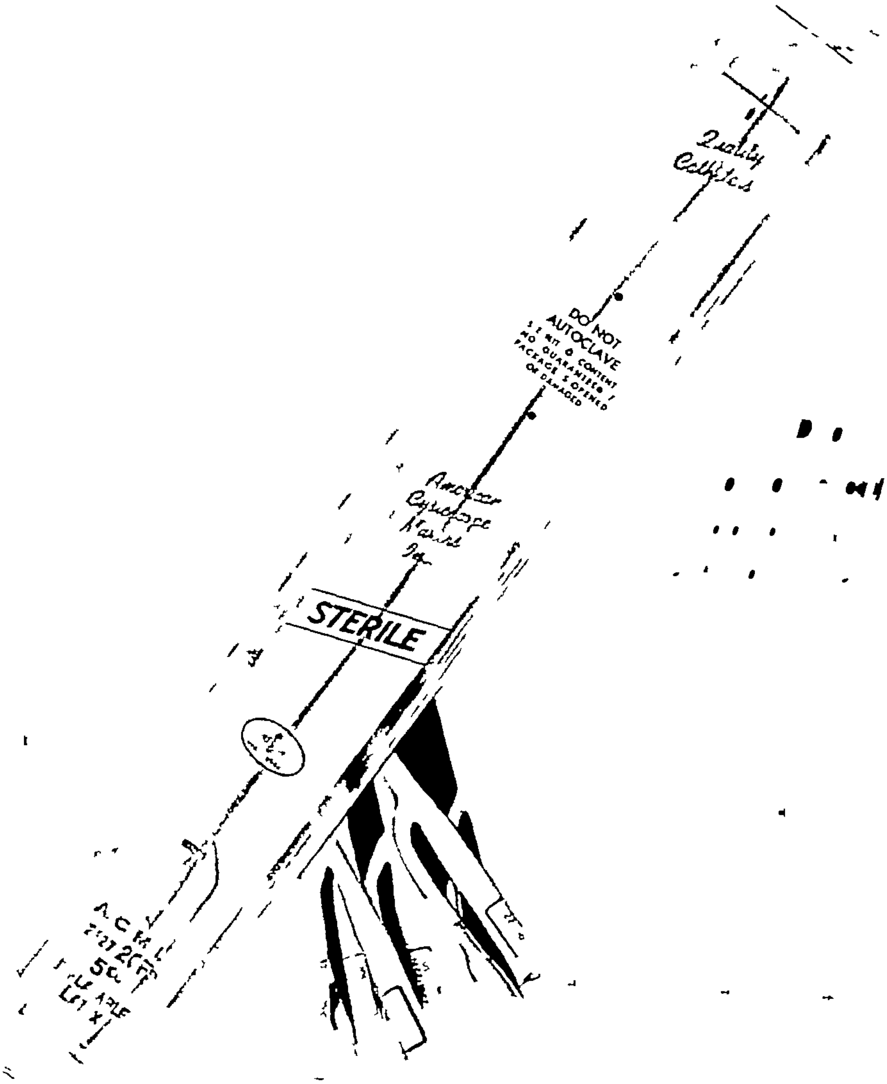
Squibb Quality—the Priceless Ingredient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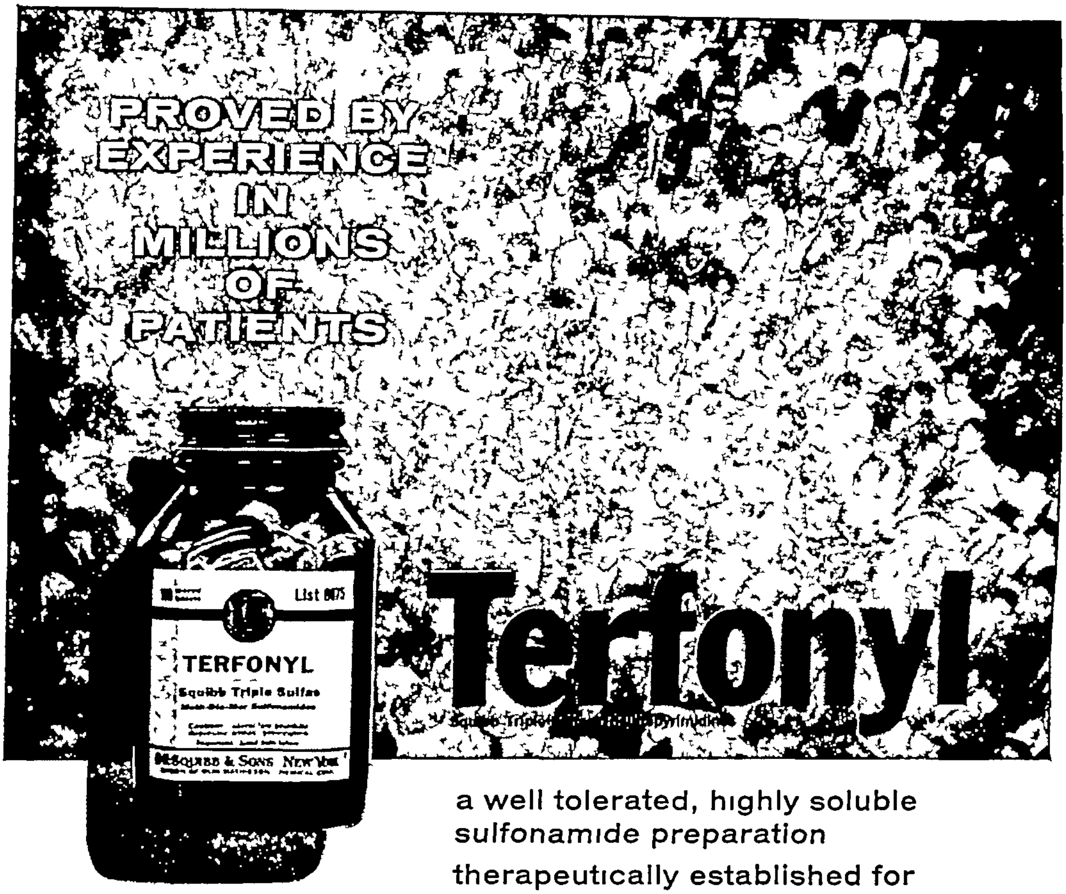
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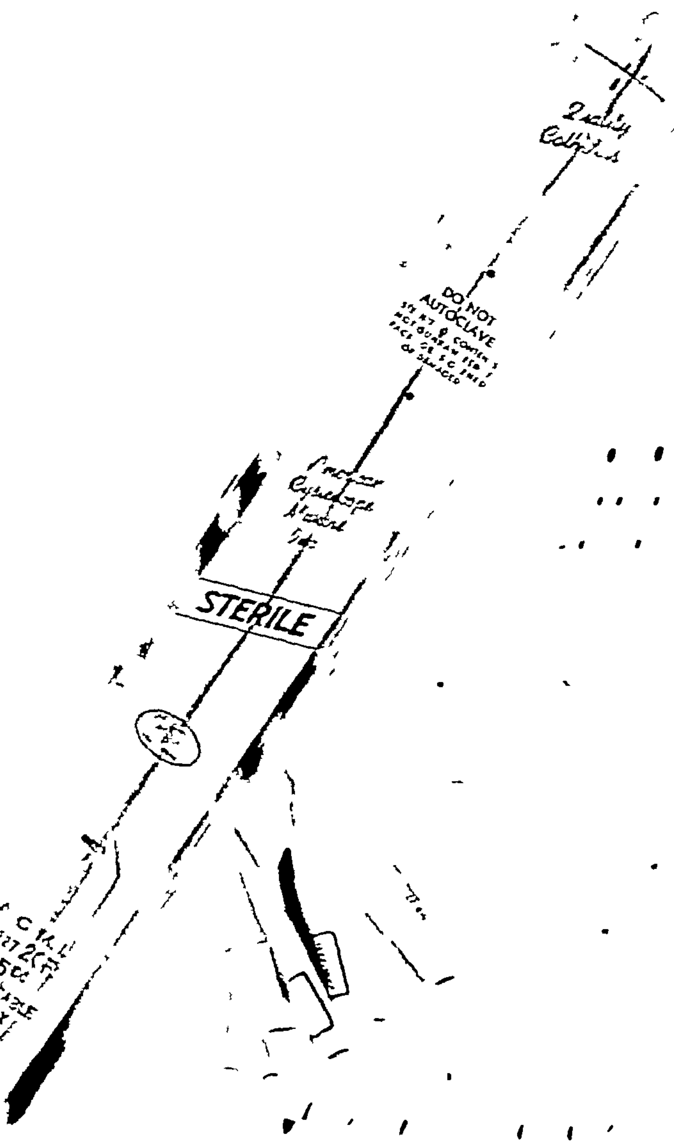

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An automatic transformer controls the incoming line voltage, regulating it in such a way as to produce maximum cutting and coagulating efficiency The automatic voltage regulator keeps voltage constant at 115 volts even when incoming line voltage varies between 80 and 135 volts It eliminates poor results sometimes caused by low line voltage

Increased Power Output

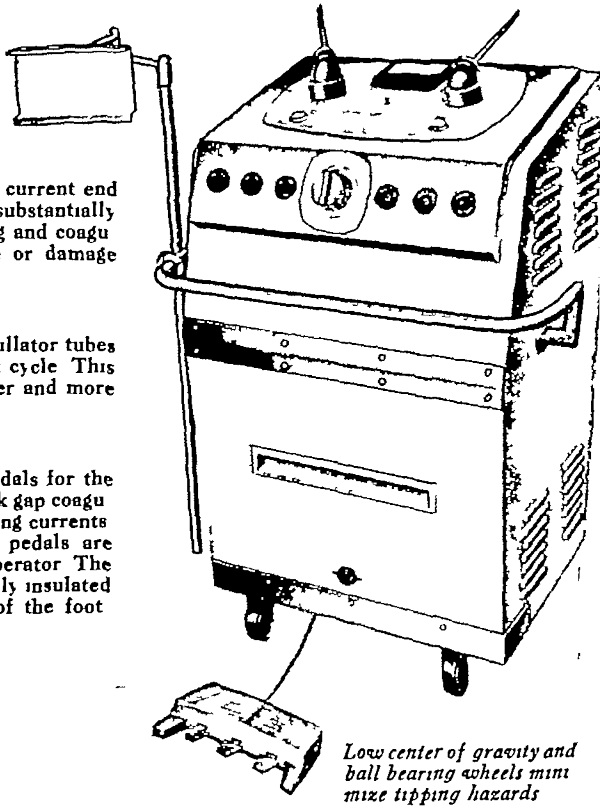
The power output on the vacuum tube cutting current end of the spark gap coagulating current has been substantially increased to give maximum efficiency in cutting and coagulating without excessive destruction of tissue or damage to instruments

Increased Cutting Speed

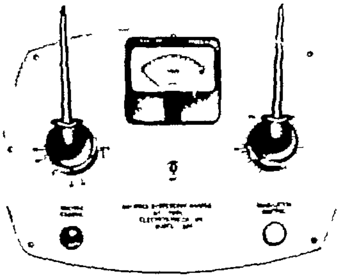
Full wave rectification is obtained by use of oscillator tubes utilizing both waves of the alternating current cycle This produces a full wave form pattern with a faster and more uniform cutting speed

Triple Pedal Footswitch

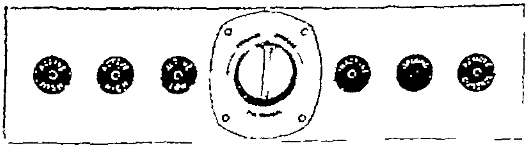
The footswitch provides three separate foot pedals for the control of the vacuum tube cutting current, spark gap coagulating current and blend of cutting and coagulating currents The switch has a broad metal base and the pedals are located in a position most convenient for the operator The connecting cord at the base of the switch is heavily insulated and of sufficient length to permit positioning of the foot switch at a convenient location on the floor



Low center of gravity and ball bearing wheels minimize tipping hazards



Volt meter on control panel shows output voltage at all times, automatic regulator keeps output constant at 115 volts even when incoming voltage varies between 90 and 135 volts Handles control power of cutting and coagulating currents and pilot lights indicate which type of current is in use



Knob on front of unit provides the extremely fine control of cutting current necessary in brain surgery and in retinal detachment operations

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THE JOURNAL OF UROLOGY
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BILATERAL PHEOCHROMOCYTOMA IN A 12-YEAR-OLD BOY

CHARLES A LINKE, IRA ROSENTHAL AND JOSEPH H KIEFER

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Pheochromocytoma is an uncommon tumor, but it is an important diagnosis to keep in mind in consideration of the patient with hypertension Untreated many patients will die of the renal, cerebral and cardiac effects of the pheochromocytoma Surgical procedures are poorly tolerated by patients having this disease when it is unrecognized The surgical treatment of pheochromocytoma has been considerably improved in recent years due primarily to experience which has been gained with adrenergic blocking agents, blood pressure sustaining agents and adrenal-cortical replacement substances during surgical work on these tumors

A more general name for the tumors is chromaffinoma with "paraganglioma" being the term generally used to designate an extra-adrenal site and "pheochromocytoma" indicating an adrenal site of the chromaffin tumor The tumors are often multiple and extra-adrenal sites are quite common The most common extra-adrenal sites are the paravertebral areas and the area of bifurcation of the aorta Tumors of this sort have also been found in the thorax on occasion

Most of the tumors are benign in the sense that they do not infiltrate and do not metastasize, but the physiological effects can be and often are, quite malignant The hypertension is, on occasion, paroxysmal but many of the patients have sustained hypertension and often it is found that the paroxysms consist of elevations of blood pressure to frightening levels in a patient who already is hypertensive

In the pediatric age group, which is arbitrarily defined as being less than 14 years of age, 34 cases of pheochromocytoma have been reported * Nine of these patients have had bilateral involvement of the adrenals Twenty-eight of the total of 34 patients have come to surgery with 18 recovering and 10 of the surgical procedures ending as fatalities This is an over-all surgical mortality rate of 36 per cent in the total group of 34 cases Prior to the present case, 9 cases of bilateral pheochromocytoma in children have been reported Six of these have come to surgery, and all of these died (a surgical mortality rate of 100 per cent in the bilateral cases)

We wish to report the case of another child with pheochromocytoma who underwent surgery

Gary B , a 12-year-old boy, became ill in February 1956, with headaches and blurring of vision Urinary frequency and polyuria developed He lost 10 pounds from February until May On May 16 his headache became quite severe, and vomiting and abdominal pain commenced A physician noted that the boy had severe hypertension and arranged hospitalization in Kankakee On admission, the blood pressure was 170/120 Urinalysis was negative Blood urea nitrogen

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Read at annual meeting of North Central Section of American Urological Association, Mackinac Island, Mich August 29-31 1957

* Cone and associates Pediatrics, 19 44, 1957

was normal An intravenous regitine test for pheochromocytoma was performed with the injection of 3 mg intravenously The test was positive The blood pressure dropped from 180/150 to 100/60 in one minute An intravenous pyelogram was negative On the day of the intravenous pyelogram the boy became disoriented and uncontrollable His blood pressure rose to 200/170 He was given regitine, reserpine and phenobarbital and was transferred to the Research and Educational Hospital

Blood pressure on admission was 190/140 in the arms, and 220/160 in the legs Retinal findings were consistent with severe hypertension with papilledema of both discs The blood chemistry findings were normal as were the chest and abdominal x-ray films and the electrocardiogram The regitine test was repeated and again found positive There was a marked increase in noradrenalin in a 24-hour collection of urine A value of 1406 micrograms was found by Doctor Goldenberg of New York who performed the test for us

The patient was treated with oral regitine in gradually increasing dosage until he was receiving 75 mg every 2 hours Blood pressures ranged from 200/160 to 130/98 No definite pattern could be found correlating the dose of regitine to the blood pressure The ophthalmoscopic changes persisted There were no further episodes of hypertensive encephalopathy On June 5 a presacral air study was done Under local anesthesia 750 ml air was injected over a 15 to 20 minute period Roentgenograms revealed a heart shaped mass superior to the upper pole of the right kidney No mass was seen on the left side

On June 7 the patient was taken to surgery The eleventh rib on the right was resected and the retroperitoneal area entered by reflecting the pleura upward and cutting the lower portion of the diaphragm This afforded excellent exposure of the right adrenal which was markedly enlarged by the presence of a tumor which measured 6 cm in diameter The right adrenal including the tumor was resected without difficulty The blood pressure fell after removal of the tumor to 140/100, but no norepinephrine was administered The peritoneal cavity was opened but no other tumor was found by palpation—including the area about the bifurcation of the aorta and the area of the left adrenal The patient tolerated the procedure well The tumor was found to be a pheochromocytoma It contained 2 mg per gm of norepinephrine and it weighed 30 gm

Three days after surgery hypertension was again noted, and a week after surgery the blood pressure rose to 200/130 on one occasion The intravenous regitine test was repeated and found to be positive for pheochromocytoma A 24-hour collection of urine contained 2020 micrograms of norepinephrine, a finding consistent with pheochromocytoma Oral regitine was resumed On June 18 intramuscular cortisone was administered, and on June 19 the child was taken to surgery During induction of the anesthesia with pentothal and cyclopropane the blood pressure rose to 220/160 and then suddenly became unobtainable There was no heart beat An incision in the fifth intercostal space was promptly made and the heart was found at standstill with the muscle in a state of moderate contraction After 15 manual systoles the heart regained its normal rhythm and the blood pressure returned to 160/130 No further surgery was done after closure of the thoracotomy wound on that day There were no apparent deleterious effects from the episode of cardiac arrest Regitine was resumed with the reappearance of severe hypertension On July 3 the patient was again taken to surgery after injection of cortisone on the two preceding days Anesthesia was given with nitrous oxide ether and intravenous succinyl choline

A left paramedian incision was made Palpation and inspection of the right lumbar area and the area around the bifurcation of the aorta revealed no evidence of pheochromocytoma Palpation in the left adrenal was not entirely satisfactory It was elected to expose the left adrenal through the abdominal incision and the incision was extended laterally The peritoneum over the left kidney and adrenal area was opened and the left colon was mobilized medially in order to expose the kidney and adrenal area better After exposing this area it was found that just anterior and somewhat medial and quite adherent to the left kidney there was a nodular mass which dissection disclosed to be attached to the left adrenal such that only a small area of the upper portion of the left adrenal was normal in architecture grossly The lower and medial portions of the left adrenal were involved in a nodular tumor There were at least 3 nodules in this tumor and the entire tumor measured approximately 8 cm in length and about 3 cm in width and 3 cm in thickness This was resected along with the entire left adrenal without particular difficulty An area along the aorta just above the left renal vessels but not adherent to the left adrenal was biopsied because this area was somewhat thicker than the expected lymph nodes in this area should be The biopsy disclosed the tissue to be another pheochromocytoma Accordingly this mass was likewise excised. The entire left area along the aorta and vertebral bodies was examined with no further evidence of tumor With the removal of the left adrenal and associated tumor, the blood pressure dropped rapidly to 80 72 Intravenous norepinephrine (levophed) was started The patient was given 4 cc (4 mg) in 500 cc of 5 per cent glucose This was followed by 4 cc (4 mg) in 250 cc of 5 per cent glucose and by 2 cc (2 mg) in 250 cc of 5 per cent glucose The total of levophed given in about an hour was thus 10 mg The speed of the infusion was calibrated by the continuous determination of the blood pressure On completion of the operation the blood pressure was 140 90 Hydrocortisone (100 mg) was also given intravenously The patient left the operating room in good condition By microscopic examination a diagnosis of pheochromocytoma of the left adrenal with multiple paragangliomas of adjacent tissue was made

During the next 24 hours another 4 mg of norepinephrine was administered intravenously in 1000 cc of 5 per cent glucose, after which it was discontinued The patient was treated with intramuscular cortisone in gradually reducing dosage over the next week and was then given cortisone by mouth. Maintenance desoxycorticosterone acetate was introduced a few days after surgery Blood pressure became stabilized two days after surgery at 110 80 Catechol amine excretion in the urine returned to normal limits The fundi rapidly returned to normal The boy was discharged from the hospital on July 27 and has remained well He is maintained on oral cortisone 12 5 mg every eight hours and on monthly injections of desoxycorticosterone trimethyl acetate (50 mg) He is given additional table salt with his meals He has returned to school and is doing well

DISCUSSION

This case illustrates that pheochromocytoma along with renal disease, coarctation of the aorta and essential hypertension must be considered in the differential diagnosis of hypertension in children As in adults, the regitine test is valuable in diagnosis If possible, confirmation should be obtained by the determination of catechol amine excretion in the urine since false positive and negative regitine tests occur Presacral air studies may locate the tumor but cannot be relied upon to disclose the presence of all of these tumors More cases will have to be studied before the value of oral regitine prior to surgery can be ascertained It is evident that in the dosage used in this case it could not control the pathophysiological changes induced by the tumor Norepinephrine is invaluable in the maintenance of the blood pressure after the surgical removal of many of these tumors and provision for its administration should be made while planning the surgery

In considering pheochromocytoma in children it is of importance to note that these tumors are more likely to be in extra-adrenal sites than in adults, more likely to be in both adrenals than in adults, and are just as rarely histologically malignant As in adults, despite the difficulties involved, the pheochromocytoma of childhood is amenable to surgical cure

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EXPERIMENTAL UROLITHIASIS IN RAT WITH FOREIGN BODY IN THE BLADDER AND ROLE OF INFECTION IN ITS PRODUCTION

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In recent years numerous attempts have been made for production of experimental urolithiasis in animals Vermeulen and his colleagues[1] introduced a piece of zinc in the urinary bladder of rat by direct operation and stones were reported to be formed upon the zinc piece in a few weeks' time They also conducted a series of experiments following the same technique to investigate the nature of the urinary stone formation [2-7] In India similar experiments were performed by Das Pritam [8, 9]

In order to investigate the efficacy of some indigenous drugs in the prevention of urinary stone formation attempts were made in this laboratory to produce experimental stone formation following the technique of Vermeulen and his associates This group of investigators did not use any strict aseptic precaution during operation and cleansed the instruments, sutures and abdominal wall with alcohol only Following the same procedure, it was possible for us to produce stones in the urinary bladder of the most of the rats used But, the amount of stone formed and the number of cases in which stones were formed were uncertain and unpredictable in the same experimental group of animals and it was thought probable that such production of stone would not depend only on the presence of a foreign body (zinc piece) in the bladder While going through the literature on the subject, it was found that in this technique of Vermeulen, the question of inducing infection of the bladder at the time of operation as a cause of stone formation has not been completely ruled out The present work was undertaken to investigate this point particularly

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[7] Vermeulen C W and Goetz, R Experimental urolithiasis IX Influence of infection on stone growth in rats J Urol , 72 761, 1954

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[9] Das Pritam Experimental evaluation of hyaluronidase in prevention and dissolution of urinary calculi J Indian M A 28 232, 1957

EXPERIMENTS

Two groups of albino rats weighing 150–200 g from local stock were selected In the beginning of the work, only female rats were used but subsequently male rats were used almost in equal number Diet of rats in all groups consisted of wheat, salt, milk powder and water *ad libidum* The first group, comprising 14 rats, was used as control, and in this group instruments, suture and abdominal wall were sterilized with alcohol only Operations were performed under ether anesthesia Pieces of zinc to be introduced (weighing 15 to 20 mg each) were sterilized by autoclave The bladder was closed with a purse-string suture by fine cotton thread The animals were sacrificed after 4–6 weeks' time, the stones were removed, and the dry weight taken

In the second group of 18 animals, more strict measures of asepsis were maintained during the operation After each operation all the instruments were boiled in water for 15 minutes The abdominal wall was sterilized with iodine and alcohol Suturing materials and zinc pieces were sterilized in the autoclave From the day of operation until the animals were sacrificed, each animal was given daily intramuscular injection of combined penicillin and streptomycin in the 1 50 dose for an adult human being in 0 1 ml (0 5 gm streptomycin and 400,000 units of penicillin dissolved in 5 ml ie-distilled water and from that 0 1 ml was injected with a tuberculin syringe) After 4–6 weeks' time animals were sacrificed and the piece of zinc was removed, dried and weighed in the usual way

Other investigations of urine During the period of experiment, urine from individual rats and sometimes in a group of 3 rats was collected for determining the pH and in some cases the surface tension of the urine was recorded by Du-Nouy tensiometer

RESULT

In the control group of animals, in all the rats except one, stones were formed within 4–6 weeks' time Weight of the stones formed in 14 cases, excluding the weight of zinc introduced, was 3, 139, 4, 21, 286, 43, 65, 14, 3, 11, 85, 78, 44 and 0 mg In 3 of these cases there were multiple secondary stones with marked hypertrophy of the bladder

In the group treated with penicillin and streptomycin none of the rats had any measurable quantity of stone formation Excluding the weight of the zinc, combined weight of all the stones was only 12 5 mg, i e only 0 67 mg per rat In most of the cases there was slight coating of the zinc piece and in a few, there was a small yellowish deposit in one corner of the zinc

pH of urine pH of the urine of the rats also showed some characteristic difference In the control group pH varied from 7 2 to 7 8 all of them on the alkaline side, whereas in the group treated with antibiotics, pH varied from 6 2 to 7 2 only As the diet of all rats was identical the difference encountered is not due to any dietetic variation but possibly due to presence of infection in the control group

Surface tension As measured by Du-Nouy tensiometer, surface tension did not reveal any difference in the two groups of rats Surface tension was measured in the groups where female rats were used only and it varied between 42–55 dynes/cm of urine in both the groups

DISCUSSION

Precise mechanism of urinary stone formation is still obscure Collica[10] reported a few experiments in which a foreign body was placed in the renal pelvis of dogs and stated that where infection and partial obstruction had occurred, calculi were formed Vermeulen and his associates[1] claimed that experimental production of stones was possible without infection and pH change, with foreign body alone in at least one experimental animal—rat—following their technique In their experiment, out of 96 rats they found that at the time of sacrificing the animal, 40 rats showed some infection in the urine on culture Of these, 28 had stone formation and 12 did not have any In the remaining 56 rats 41 had stone formation and 15 did not In view of the fact that stone formation occurred in both the groups with the infected and non-infected urine, they did not lay any special importance on the role of infection in the production of this type of experimental urinary lithiasis and made no attempts to prevent urinary tract infection by antibiotics in the experimental animals

From the results reported in the present work, it is obvious that associated infection is the main factor in the formation of stone when zinc is introduced in the bladder of experimental animals If the infection can be controlled with adequate aseptic precaution and postoperative antibiotic therapy, stone formation can be prevented In the present work no attempt was made to culture the urine at the time of removing the stones in the control group It was believed that even a negative result after 4–6 weeks' time could not exclude the possibility of infection in the early part of experimental period and such infection may clear out spontaneously after 4–6 weeks' time But the influence of any infection in the early part might initiate the stone formation which would continue to grow once the nidus is formed Vermeulen and his associates, as has been mentioned before, did encounter infection in 42 per cent of cases but it is believed that this finding cannot exclude infection in others with spontaneous recovery in many of them after 4–6 weeks' time

In order to exclude the possibility of any infection, the present work was planned to control any infection under the cover of adequate antibiotic therapy and the result is quite convincing

Considering the fact that no reasonable quantity of stone formation was possible after introduction of a piece of zinc in the bladder of the rat, when adequate aseptic precautions were taken and when adequate antibiotic therapy was continued during the period of experiment, this technique of experimental lithiasis was considered ineffective

SUMMARY

In two groups of albino rats, experimental production of urinary lithiasis was tried by introducing a piece of zinc weighing 15–20 mg in the bladder of the

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[10] Collica, J New concept of pathogenesis of urinary lithiasis Am J Surg, 76 424, 1948

animal The animals were sacrificed after 4–6 weeks to find out the amount of stone formed

In the first group (control) of 14 rats, no antibiotic was given during the period of experiment Stones were formed in all of them except in one and weight of stones formed varied from 3 to 286 mg

In the second group of 18 rats, an adequate quantity of combined penicillin and streptomycin was given daily after operation and in none of the rats was any appreciable quantity of stone formed

Urinary pH of the first group of rats was on the alkaline side and that of the second group was on the acidic side Surface tension of the urine did not show any variation in the two groups

It is concluded that where adequate aseptic precaution is taken at the time of operation and where the whole experimental period is covered with adequate antibiotic therapy, experimental production of urinary lithiasis is not possible by introducing a piece of zinc in the bladder of the rat

Our grateful thanks are due to J C Ray, M D , F N I , director, Indian Institute for Biochemistry and Experimental Medicine, Calcutta, for his help and keen interest in this work

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CONCOMITANT NEPHRECTOMY AND PROSTATOLITHECTOMY

ALFONSO DE LA PEÑA, JOSE RUIZ A and J ARNOLD FINER*

From the Department of Urology, Faculty of Medicine, University of Madrid, Spain

It is not the purpose of this report to establish a surgical record, but rather to show the perfect tolerance of two major urological procedures on the same patient, performed consecutively as one uninterrupted surgical act

The incidence of plural pathological processes in the urinary tract is quite frequent polyps of the urinary bladder, poliquistoma renalis, stones in different location (kidney, ureter, bladder, prostate, etc), tuberculosis and cancer may be also coincidental Silent carcinoma of the kidney in patients afflicted with prostatism must always be considered if asymptomatic and persistent hematuria does not correlate with the lower tract urological findings Modern urography has increased our ability to discover or suspect silent though not always early neoplasms of the kidney, ureter and bladder, concomitant with other urological or general conditions

In the past, we have had to perform nephrectomies six times in patients with advanced prostatic syndrome, five for adenocarcinoma and once for isolated latent tuberculous cavities Fear of the burden that a prostatectomy might impose upon the patient forced us to perform the minimal transurethral cystostomy (A Peña) Therefore, the invalidism and unpleasantness of an indwelling suprapubic tube led us to consider the possibility of avoiding cystostomy in these cases

The logical aim to spare the patient from undergoing physical distress of two different surgical operations compelled us, in the following case, to perform nephrectomy plus prostatectomy and the removal of a radiolucent stone of the bladder, at the same time A smooth postoperative course and complete recovery were obtained

CASE REPORT

E V , 9207, was a man aged 65 years His father died of prostatic obstruction and his mother of diabetes He suffered diabetes, pleurisy, and tonsillitis He complained of adynamia and a weight loss of 10 kg during the past six months Three years ago, total hematuria with pain in the right dorsolumbar area, subsequently the hematuria repeated asymptomatically He had increasing urinary frequency also for the past three years, on admission he was voiding every 15 minutes during the day and from four to six times at night, with urgency and terminal dysuria, but no fever

The right kidney was palpable and tender Rectal examination revealed an enlarged, benign prostate with free borders, estimated weight 30 gr External genitalia were normal The general physical examination was negative The patient weighed 78 kg On January 15, 1958, the patient weighed 87 kg

Accepted for publication June 3 1957

* Present address Youngstown, Ohio

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The urine on microscopic examination showed abundant red cells, some leukocytes and epithelial cells of the high passages Albumin 0 28 gr No glucose Red blood cells 4,800,000, white blood cells 9,400, E S R , 15–32, KI, 15,5, urea 81 mg , glucose 148 mg per cent, acid phosphatase 0,98 u

A plain x-ray did not show any stone or abnormalities Intravenous urography showed a half moon deformity shadow with displacement of the renal pelvis to the middle line of the right side The shadow of the upper pole of this kidney was also denser The upper calyces were not visualized and the lower calyces were compressed and distorted The left kidney appeared normal urographically

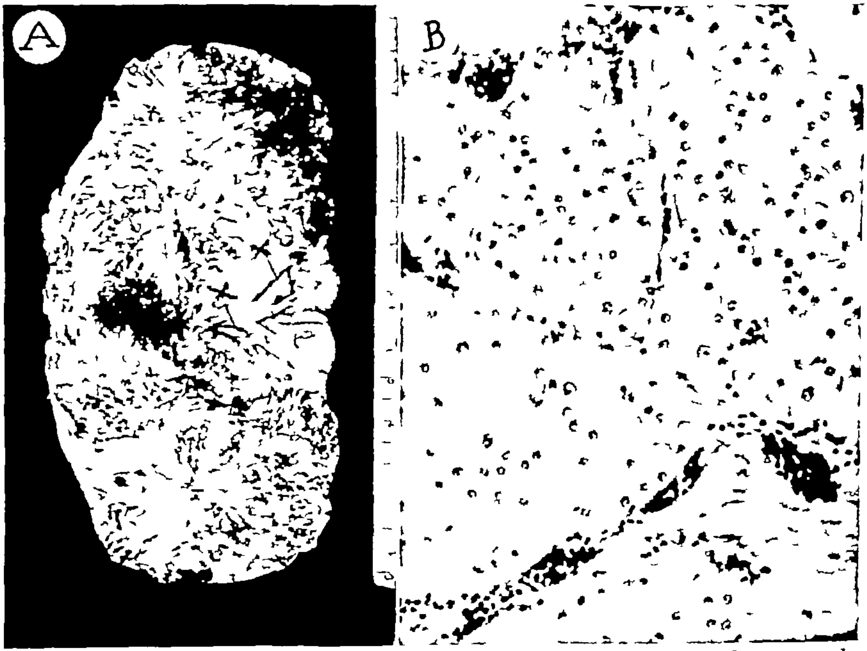

FIG 1 *A*, specimen of right kidney reveals neoplasm *B*, histological section shows clear cell adenocarcinoma grade 2–3 (Broders)

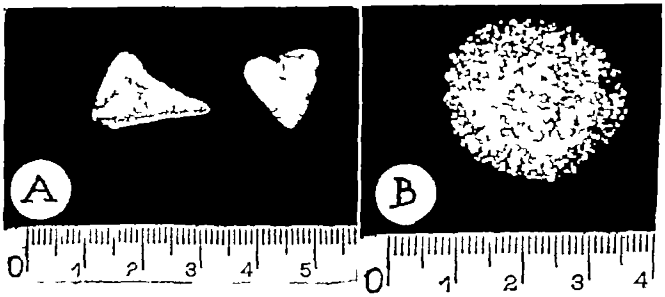

FIG 2 *A*, two small kidney stones *B* medium size bladder stone

Cystography showed some intravesical protrusion of an enlarged prostate, there were no signs of infiltrating lesions in the bladder

Under spinal anesthesia a cystoscopy was performed, the bladder capacity was 110 cc A large uric acid stone was discovered There was no evidence of vesical neoplasm Subsequent to cystoscopy right lumbotomy was performed followed by right nephrectomy for a macroscopically malignant tumor of its upper pole The procedure required 40 minutes Considering that the patient needed immediate attention for his vesical condition, the anesthesiologist and the hematologist agreed on proceeding with the prostatectomy with no undue risk The bladder stone was removed suprapubically, and then the fibroadenomatous prostate was enucleated rapidly and easily One hour and ten minutes were spent for both stages Hemostasis was good The patient was up and around on the third postoperative day One 300 cc blood transfusion was given to improve his general state On the ninth postoperative day the urethral catheter was withdrawn and the patient has urinated normally since On the eighteenth postoperative day, the patient was discharged At the present time he feels normal

Histopathological report (Prof Fernando de Castro) The specimen was a right kidney A large ovoid mass replaced the normal kidney substance which was preserved only in the lower pole The upper pole measured 6 by 7 cm , was round and corresponded in color and gross characteristics with a solid renal tumor (fig 1, *A*) Weight 1 400 gr Hemisection disclosed two small stones in the kidney pelvis (fig 2 *A*) Microscopic study dense hypernephroid adeno-

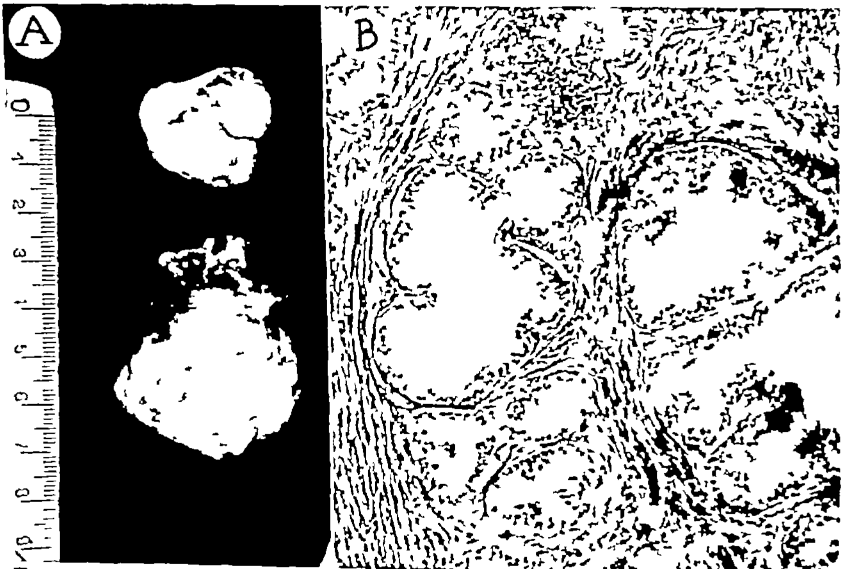

FIG 3 *A*, benign adenoma of prostate, weight 48 gr *B*, histological section benign adenoma

carcinoma, probably of tubular origin (fig 1, *B*), acid uric stones Prostate typical adenoma, weight 48 gr (fig 3, *A*) Microscopic study benign adenomyoma with inflammatory lymphocytic infiltration (fig 3, *B*) Bladder stone medium size, 3 by 4 cm , rounded showing typical gold color and rough surface (fig 2, *B*), uric acid in nature

It was the meticulous evaluation of the surgical risk, and adequate operative preparation plus the benefit of having a competent anesthesiologist, as well as recuperating and resuscitating teams, which made less hazardous these two major concurrent surgical acts In addition, simplicity of both stages, plus unusual short time in accomplishing the nephrectomy as the main indication, led us to decide on adenomectomy plus removal of the bladder stone, though we undertook it with very much concern, for the increased operative risk This personal concern for a surgeon was largely repaid by a normal postoperative course

Padilla 22, Madrid, Spain

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REGIONAL HYPOTHERMIA IN ACUTE RENAL ISCHEMIA

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In recent years, during the course of extensive renal and vascular surgery, the renal blood flow has been frequently interrupted for more protracted periods than heretofore. At the present time sufficient laboratory data are available to suggest that there is a limit to the period of temporary renal anoxia compatible with survival.[1] [2] [3] This limit, which varies from species to species, may be measured by survival of an animal or histological examination of the organ when anoxia has been unilateral.

Litten,[4] in 1880 demonstrated that the renal pedicle could be occluded for one hour before microscopic damage could be observed upon subsequent section. Eisendrath and Strauss[5] in 1910 studied the changes in the kidneys of rabbits and found residual evidence of injury occurring four weeks after a period of fifteen minutes of temporary anoxia. George Prather[6] has suggested the clinical use of a rubber-shod pedicle clamp to occlude the renal hilar vessels during the removal of large branching calculi, but cautioned that such should be released at eight to ten minute intervals.

Longer periods of anoxia were recently studied by Van Slyke and associates[1] using previously unilateral nephrectomized dogs. In their experiments occlusion of the renal artery and vein for three hours resulted in a brief period of anuria followed in two to three days by a gradual rise of the blood urea nitrogen to approximately 150 mg. per 100 ml. By the fourth day however, a gradual return to normal levels was noted. Survival in this group was close to 100 per cent. If the period of anoxia was extended to four hours 50 per cent of the animals died and if extended to six hours, the mortality was 100 per cent. There is little doubt that occlusion of both artery and vein appears to be better tolerated than occlusion of the vein alone, as demonstrated by C. W. Vermeulen.[7]

It is possible that pre-existing renal damage enhances the likelihood of increased injury by anoxia, and a relatively brief period of anoxia in an already diseased kidney may be equivalent to a much longer period in the normal organ. There-

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Read at annual meeting of North Central Section of American Urological Association, Mackinac Island, Mich., August 29–31, 1957.

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fore, an attempt was made to utilize the effect of regional hypothermia to decrease tissue oxygen demands during periods of renal ischemia Generalized hypothermia, while desirable in some situations, carries with it certain side effects which are significant and which may be avoided by localized cooling It is technically difficult to produce generalized hypothermia Even with moderate degrees of cooling, cardiac irregularities are common To produce temperatures adequate to protect the kidney from anoxic damage, as found necessary in our experiments, fibrillation and cardiac standstill would result The rewarming of the entire body is a tedious process and several complications may arise at this point again, the complete derangement of the temperature regulating mechanisms has been frequently observed

Although the literature concerning generalized hypothermia is abundant, only recently attention has been paid to the effects of hypothermia on renal function [8] A few reports deal with the survival and late effects of hypothermia during the periods of renal pedicle occlusion Utilizing generalized hypothermia Hársing, Jellinek and associates[9] in Budapest, Hungary in 1956 reported a 100 per cent survival following a four-hour period of renal pedicle occlusion when the rectal temperature of dogs had been lowered to 22 to 24 degrees centigrade The same group reported a 30 per cent survival in non-cooled animals Localized hypothermia has been applied to renal autografts in sheep by Mitchell and Woodruff[10] in New Zealand with interesting results In these transplanted kidneys, when the renal temperature was above 25 degrees centigrade, all the animals died after a two-hour period of ischemia All the animals survived however, if the kidney was locally cooled to between 10 and 20 degrees centigrade

The purpose of our study was to re-define the period of renal anoxia that is compatible with survival in the dog Secondly, the effects of regional cooling of the kidney during prolonged periods of acute renal ischemia were followed and correlated with the survival of the animals, the histological changes found in the kidney, and with the course of the blood urea nitrogen Thirdly, an attempt was made to pinpoint the optimum temperature for kidney survival during and following the anoxic period

PROCEDURE

Adult mongrel dogs underwent right nephrectomy at least two weeks prior to the experimental period Under general intravenous sodium pentobarbital anesthesia the remaining left kidney was delivered through a muscle-splitting left lumbar incision The perirenal fat was stripped from the capsule, and any communicating capsular vessels tied The ureter was dissected free from the pedicle, and then the artery and vein were stripped of some, but not all, of the fat nerves To combat intrarenal thrombosis, 1 cc heparin diluted with 4 cc of

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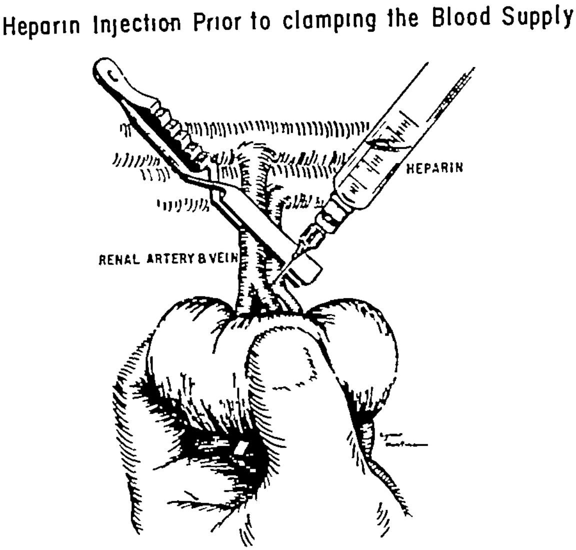

FIG 1 Technique of injection of renal artery with heparin solution with clamp in position for immediate application

normal saline was injected into the renal artery immediately before a "bulldog" rubber-shod clamp was closed on both artery and vein (fig 1) An additional clamp secured the tips of the "bulldog" to insure complete occlusion of the pedicle Temperature of the kidney was recorded by means of a small glass thermometer inserted through a stab wound into the renal substance Room temperature and rectal temperature were recorded continuously throughout the procedure Each animal received 500 cc of 5 per cent glucose in distilled water intravenously during the period of occlusion which lasted six hours in every instance At the end of the six-hour period, the "bulldog" clamp was released, pulsation was palpated in the segment of the artery distal to the clamp and filling of the vein was observed The kidney was then replaced in the renal fossa, the wound closed and the dogs followed until death or sacrifice At this time, the renal size was measured and compared with measurements obtained prior to the period of acute anoxia The kidneys were then fixed and submitted for pathological study

In the control group of 10 dogs, the kidney was left exposed to room temperature covered only by a gauze sponge and protected from the warmth of the animal by an asbestos pad In the experimental group of 10 dogs, the kidney was cooled during the period of anoxia by a plastic jacket* surrounding the kidney but similarly insulated from the animal (fig 2, *A*) By means of a continuous flow of cold water regulated by rate and temperature, we were able to keep the temperature between 20 and 25 degrees centigrade during the period (fig 2, *B*) The kidneys of the third group of animals underwent additional lowering of the temperature to 10 to 15 degrees centigrade by circulation of a salt and water mixture through the plastic jacket

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* Plastic Dispoza Bag (C R Bard, Inc , Summit, N J)

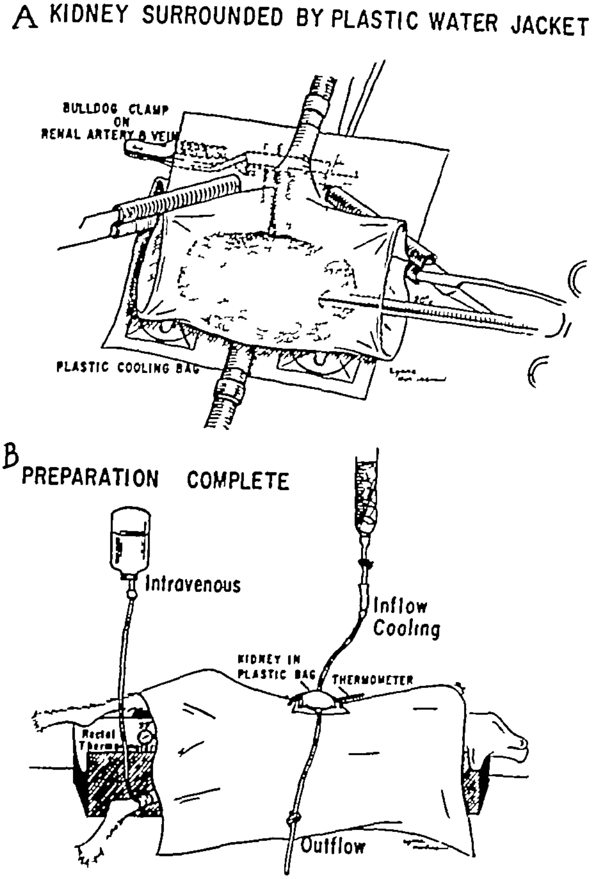

Fig 2 *A*, experimental kidney surrounded by plastic jacket through which cooling solution flows *B*, experimental animal with thermometer in kidney, rectum and with cooling solution flowing through plastic jacket Longest and shortest days of survival for control and experimental groups

Blood urea nitrogen was used to follow renal function during the procedure and subsequent days A blood urea nitrogen was drawn at the start and end of the acute period of anoxia and daily for the next four days Subsequent readings were taken at three to seven-day intervals

RESULTS

In the control series, at the end of a six-hour period of anoxia, the kidney appeared dark-blue, mottled and devitalized After release of the pedicle clamp, the general appearance improved with oozing from the surface vessels and the site of the temperature recording incision This bleeding was easily controlled with mattress hemostatic sutures in all cases before the kidney was replaced in the wound The dogs of this group usually went through a period of anuria of one to two days' duration followed by a gradually increased urinary output The animals appeared lethargic and frequently refused to eat Usually by the third day they would take a small amount of milk or water Nevertheless, there was a 100 per cent mortality with death usually occurring in four to five days In the experimental group where the renal temperature was reduced to 20 to 25 degrees centigrade, 30 per cent of the animals survived and were sacrificed after eight weeks In group three, in which the kidney temperature was dropped even lower to between 10 and 15 degrees centigrade, a 75 per cent survival was found A remarkable difference in gross appearance of the kidney at the end of the six-hour period of ischemia was noticed after cooling at either level Instead of being dark-blue and mottled, the kidney appeared rather pale, smaller than normal and pinked up upon release of the pedicle much more rapidly than in the control group After a few minutes, the kidney returned to its preoperative size, and at the time of sacrifice, the kidney's gross measurements were equal

TABLE 1 *Longest and shortest days of survival for control and experimental groups*

	Shortest Day Survival	Longest Day Survival
Group 1	2	15
Group 2	5	60+
Group 3	12	60+

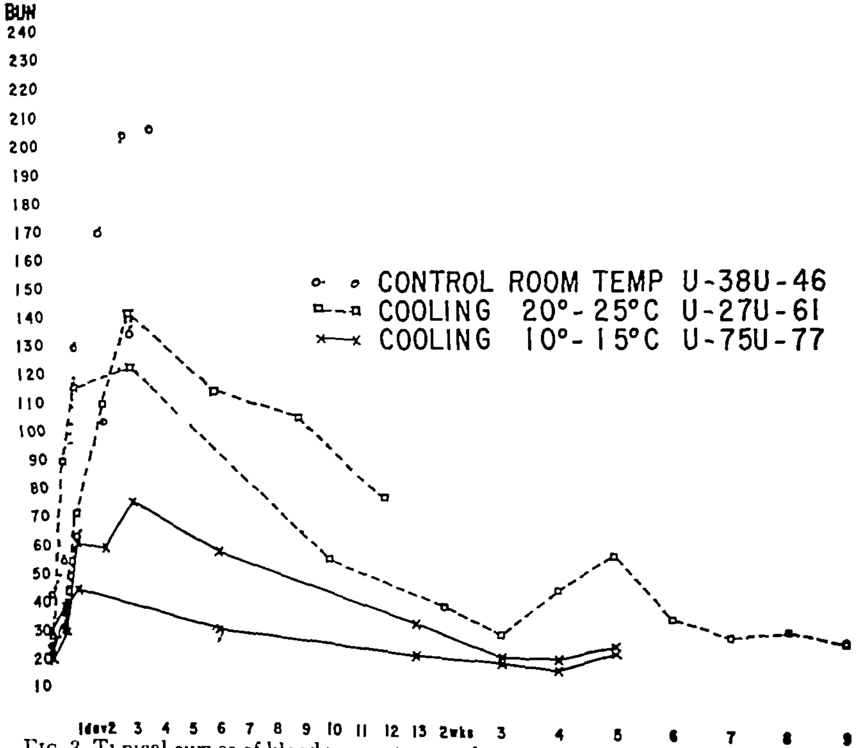

FIG 3 Typical curves of blood urea nitrogen changes in each group Blood urea nitrogen of control animals shows rapid rise until death Curve for experimental group demonstrates gradual recovery until normal values are obtained

to the size postoperatively Survival periods in terms of the shortest and longest duration of survival for each group are shown in table 1

The blood urea nitrogen in the control group showed a rapid elevation which usually continued to rise until death In the 20 to 25 degrees centigrade kidneys there was also a rapid rise, which usually declined slowly after four days In the last group, the rise was more gradual, the peak was lower and the normal levels were again obtained after two weeks In *figure 3* two representative curves are shown for each group

PATHOLOGICAL OBSERVATIONS

All but two of the control animals were autopsied within one week after the six-hour period of complete renal ischemia The kidneys presented a bulging cortex with indistinct architectural pattern The medulla was usually dark red in its entirety or in the outer juxtacortical portion The kidneys of the experimental dogs, most of which were examined within twelve days after the period of ischemia, were either pale throughout and slightly enlarged or within normal

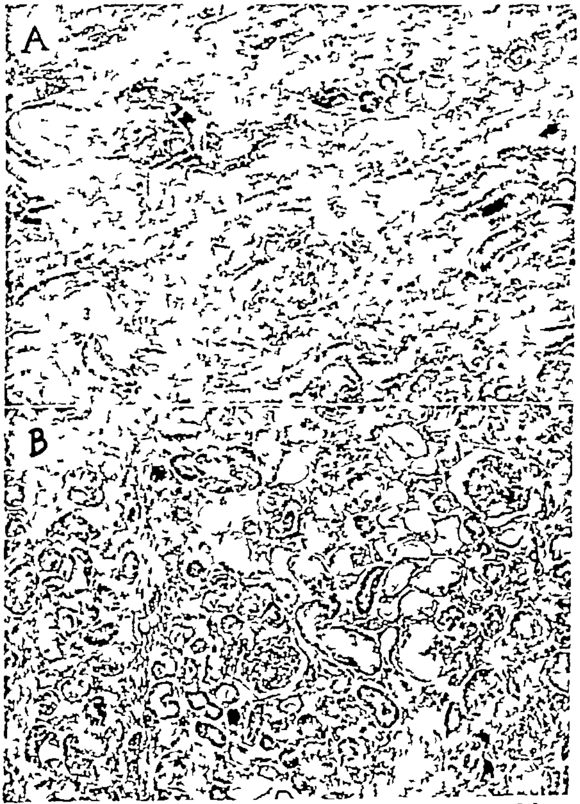

FIG 4 *A*, massive tubular necrosis in control dogs 3 days after a 6 hour period of complete renal ischemia *B*, marked tubular necrosis in control dog 3 days after a 6 hour period of complete renal ischemia H & E × 126

limits in gross appearance and size An occasional animal in both control and treated groups showed small recent cortical infarcts

Microscopically, in all animals which died the principal lesion consisted of coagulation necrosis of the proximal convoluted tubules There was desquamation of the lining cells, loss of nuclei, and blockage of lumens by coarse acidophilic debris Superimposed calcific deposit was frequently observed The glomeruli were essentially intact and neither the loops of Henle nor the distal convoluted segments of the nephron participated in the necrosis Homogeneous pink-staining casts were numerous, especially in the collecting tubules There were focal regions of interstitial lymphocytic exudate in the vicinity of necrotic tubules

In the control dogs, almost all of which died within a few to several days after circulation was restored, the tubular necrosis was widespread and massive (fig 4, *A*) The entire proximal tubule was involved, including the descending or spiral segments, and repair was usually minimal or slight (fig 4, *B*) The necrotic lesion in the experimental animals was similarly but uniformly less

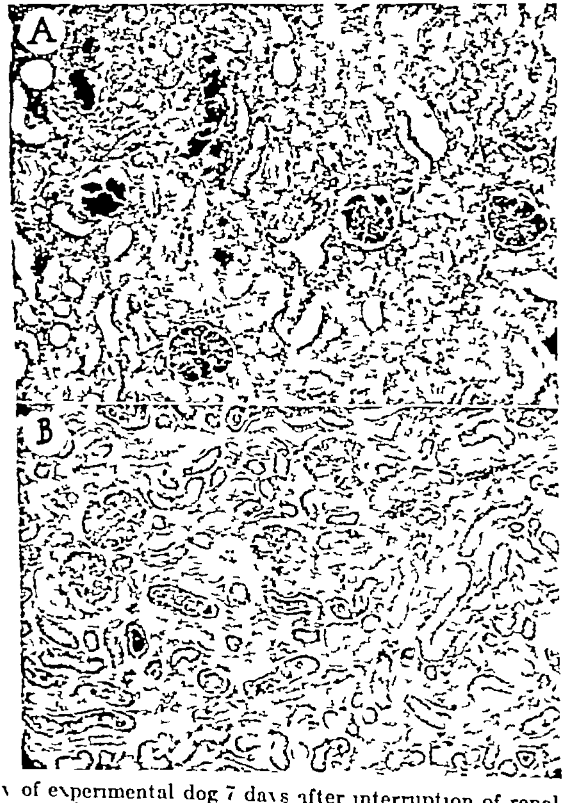

FIG 5 Kidney of experimental dog 7 days after interruption of renal circulation for 6 hours Slight necrosis of tubules largely repaired and focal calcific deposit *B*, kidney of experimental dog 8 days after interruption of renal circulation for 6 hours Slight tubular necrosis with repair H & E × 126

severe in extent and distribution In fact, in most instances the renal damage was comparatively slight or minimal and consisted merely of focal degeneration or necrosis of the proximal tubules (fig 5, *A*) Widespread massive tubular destruction did not occur in any of the animals Repair was fairly rapid and within one or two weeks debris was cleared and new cells lined the dilated tubules There was focal calcific deposit Dogs sacrificed eight weeks after renewal of the renal circulation showed practically normal kidneys (fig 5, *B*)

DISCUSSION

These studies therefore demonstrate conclusively that localized cooling offers protection in the face of a severe, protracted period of renal anoxia The percentage of survival of these animals, the less severe elevation of the blood urea nitrogen with hypothermia, and the microscopic evidence of less severe injury are consistent throughout Although this is a preliminary report, and further levels of cooling are to be explored, these data to date suggest that temperatures from 10 to 15 degrees offer the maximum protection This degree of cooling, which could not be attained by generalized hypothermia without derangement of the body temperature control centers, or the development of cardiac arrhythmias, could easily be attained at surgery In the large aortic aneurysms involving the renal vessels or in dissecting aneurysms its application might prove efficacious in avoiding the oliguria and anuria seen subsequently[10] The urologist, in the case of large branching calculi, where extensive nephrotomy is indicated, or in the segmental replacement of renal arteries, similarly might find it effective

It is possible that in certain situations combined generalized and regional hypothermia may be used concomitantly This might be especially applicable in the case of the previously mentioned large abdominal aneurysms when separation of the kidney from its blood supply is necessary during aortic replacement It seems unlikely that its use can successfully be extended to the clinical situations of anuria, the so-called acute tubular necroses, where the microscopic picture is so similar Here the difficulty of achieving regional cooling in a critically ill patient would prohibit its usefulness If renal homotransplantation becomes a clinical reality, cooling the graft may aid in its survival

Prolonged studies are contemplated to determine if ultimate renal dysfunction and hypertension will develop Also, it is hoped to ascertain if cooling will protect the already damaged kidney during various manipulative procedures In general, we feel that regional hypothermia is a potentially valuable tool for the urological surgeon

SUMMARY

A six-hour period of acute renal ischemia at room temperatures results in 100 per cent mortality in the dog

In experimental groups, with applied regional hypothermia (20° and 10°C) 30 per cent and 75 per cent survival was achieved

Histological studies showed proximal tubular damage with less severe degrees of injury in the cooled group

Renal function measured by blood urea nitrogen levels showed a significant protection afforded by hypothermia during the period of anoxia

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EXPERIMENTAL HYDRONEPHROSIS PRODUCED BY BETA IRRADIATION OF THE URETER

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In the course of experiments designed to study the effect of ureteral obstruction on the susceptibility of the kidney to infection, complete ureteral ligation proved an effective method of producing such infection following intravenous injection of bacteria.[1] Although this model was satisfactory, for observations on the early evolution of the disease process, the progressive anatomical changes associated with complete ureteral ligation prevented adequate study of the chronic infection. It was desirable, therefore, to develop a means of causing slowly progressive, partial ureteral obstruction. A method by which uniform injury could be given directly to the ureter with resultant scarring and partial obstruction was suggested by the availability of beta-emitting isotopes of known half-life, without complicating gamma producing isotopic contaminants or gamma producing daughters.

These experiments describe the course of hydronephrosis produced in the rat following direct irradiation of the ureter.

MATERIALS AND METHODS

Animals. White, male, Sprague-Dawley strain rats, weighing 150–250 gm. were used.

Ureteral obstruction. Animals were anesthetized with 10–20 mg. pentobarbital sodium administered intraperitoneally, supplemented as necessary. After the hair of the left flank area had been removed with electric clippers and operative site cleansed with 70 per cent ethyl alcohol, a 2 cm. incision was made just below and parallel to the left lower rib margin. The ureter was identified and a small segment, approximately 2 cm. from the ureteropelvic junction, was freed from surrounding tissue and supported by a smooth, rounded wooden stick. A strontium^{90} applicator (tracerlab) was then placed against the ureter with gentle pressure for the required length of time. This applicator contains 100 millicuries of strontium^{90} uniformly distributed in a circular area with an active diameter of 5.0 mm. It is a pure beta particle emitter with an output of 102.6 rep (roentgen equivalent physical) per second at the surface. Consequently the stated dose to the ureter is plus or minus about 100 rep because of the difficulty of gauging exposure by hand to less than one second. After desired irradiation had been given, applicator and wooden stick were removed and ureter carefully returned to its normal position. The peritoneum was approximated with interrupted cotton sutures and skin wound closed with metal clips.

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* Research Fellow of the American Heart Association. Present address: Department of Medicine, Veterans Administration Hospital, Los Angeles, Calif.

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Control animals were subjected to the same operative procedure, but instead of direct application of strontium^{90}, a smooth metal surface, similar to the tip of radioactive applicator, was placed against the ureter for one minute

Intravenous pyelograms After the animals were anesthetized with intraperitoneal pentobarbital sodium, 2 ml of a 50 per cent solution of diatrizoate sodium (hypaque, Winthrop Laboratories, New York, N Y) was injected intravenously into a tail vein Preliminary observations had indicated that satisfactory pyelograms were obtained 20 to 30 minutes after the injection of dye and all films reported in this paper were taken during this interval The technique for exposing the films was 31 KVP at 30 milliampere-seconds at 72 inch distance using par speed intensifying screens Pyelograms were obtained at weekly or bimonthly intervals for a period of up to four months The animals and films were marked to permit the observation of serial changes in each animal As a basis for comparison of individual pyelograms, the following grading was employed

Grade	*Description of Pyelogram*
1	Normal urogram
2	Increased density of contrast medium in pelvis as compared to normal side
3	Minimal distention of pelvis and proximal ureter
4	Moderate to marked distention of pelvis and proximal ureter
5	No opacification of pelvis or proximal ureter, enlarged kidney shadow, with or without nephrogram

This grading represents a trend of change rather than absolute values, and as such, seems adequate

Histologic examination of tissues Animals were anesthetized with intraperitoneal pentobarbital, the abdomen opened and kidneys examined in situ The kidneys were removed, placed in 10 per cent neutral formalin, and after fixation were stained with hematoxylin and eosin

RESULTS

Renal changes following compression of ureter for one minute (control group) To evaluate the role of mechanical trauma in the production of the hydronephrotic changes seen in irradiated animals, the left ureter in eight rats was compressed between a wooden stick and a smooth metal non-radioactive surface with the same degree of force as was applied with the strontium^{90} applicator The results observed are shown in figure 1, *A* All animals exhibited transient hydronephrosis as noted by intravenous pyelography Changes occurred one day after ureteral compression (grade 3), persisted for seven days and then gradually subsided Animals examined at 10 days and again at 30 days had normal pyelograms

Renal changes following exposure of ureter to 300 rep In eight animals, 300 rep was administered directly to the ureter and subsequent changes were followed by intravenous pyelography All of the animals developed hydronephrotic changes of degree and duration similar to those noted following mechanical

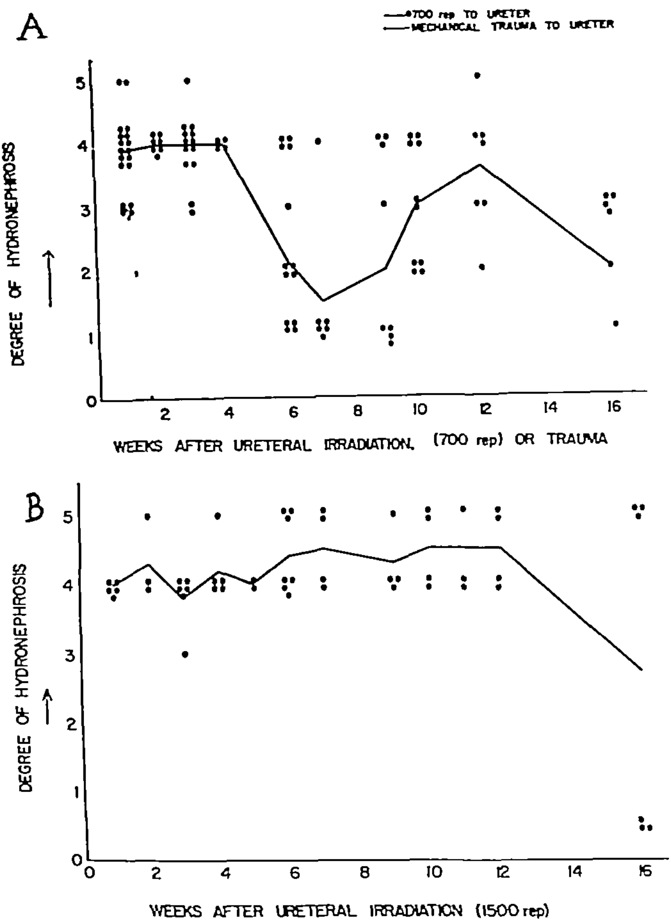

FIG 1 *A*, degree of hydronephrosis (as measured by intravenous pyelogram) produced by 700 rep administered directly to ureter Effects of mechanical (non radioactive) trauma are shown Curves represent arithmetic mean of values obtained at a given time B, degree of hydronephrosis (as measured by intravenous pyelogram) produced by 1500 rep administered directly to ureter Curve represents arithmetic mean of values obtained at a given time

trauma Pyelograms in these animals were normal when examined at 10 and 30 days following irradiation

Renal changes following exposure of ureter to 700 rep Twenty rats received 700 rep directly to the left ureter and the course of renal changes followed by intravenous pyelography at weekly or bi-monthly intervals for four months Figure 1 shows the results observed It should be noted that maximum hydronephrotic changes were seen one week after irradiation and persisted to the fourth week Thereafter a decline occurred until the seventh to eighth week when a secondary rise began which reached its peak about 12 weeks after exposure to beta irradiation Figure 2 shows a pyelogram illustrating grade 4 hydronephrotic changes in the left kidney of a rat seven weeks after irradiation

Control animals were subjected to the same operative procedure, but instead of direct application of strontium^{90}, a smooth metal surface, similar to the tip of radioactive applicator, was placed against the ureter for one minute

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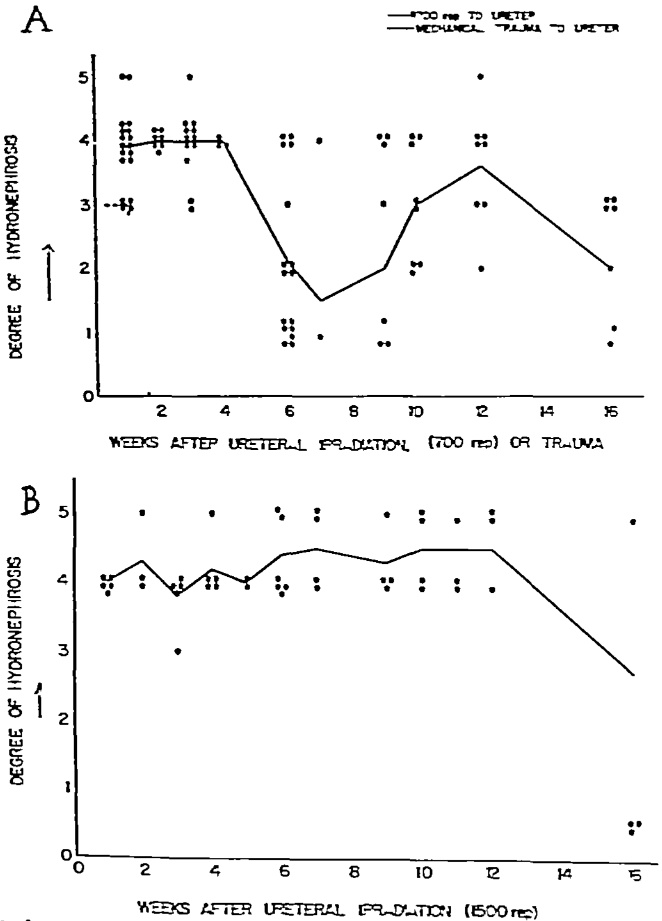

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Renal changes following exposure of ureter to 300 rep In eight animals, 300 rep was administered directly to the ureter and subsequent changes were followed by intravenous pyelography All of the animals developed hydronephrotic changes of degree and duration similar to those noted following mechanical

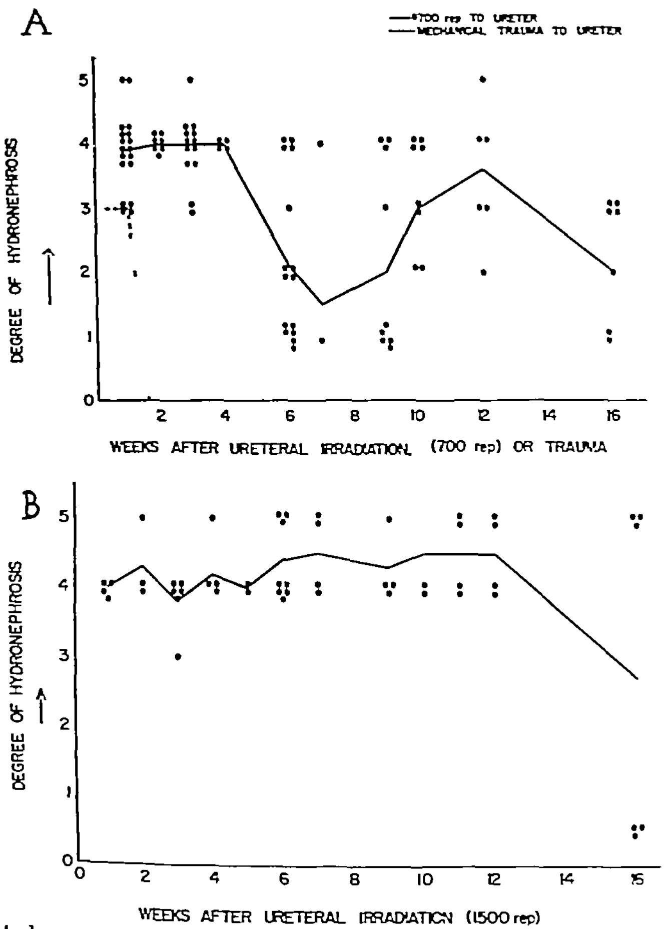

FIG 1 *A*, degree of hydronephrosis (as measured by intravenous pyelogram) produced by 700 rep administered directly to ureter Effects of mechanical (non radioactive) trauma are shown Curves represent arithmetic mean of values obtained at a given time *B*, degree of hydronephrosis (as measured by intravenous pyelogram) produced by 1500 rep administered directly to ureter Curve represents arithmetic mean of values obtained at a given time

trauma Pyelograms in these animals were normal when examined at 10 and 30 days following irradiation

Renal changes following exposure of ureter to 700 rep Twenty rats received 700 rep directly to the left ureter and the course of renal changes followed by intravenous pyelography at weekly or bi-monthly intervals for four months Figure 1 shows the results observed It should be noted that maximum hydronephrotic changes were seen one week after irradiation and persisted to the fourth week Thereafter a decline occurred until the seventh to eighth week when a secondary rise began which reached its peak about 12 weeks after exposure to beta irradiation Figure 2 shows a pyelogram illustrating grade 4 hydronephrotic changes in the left kidney of a rat seven weeks after irradiation

Renal changes following exposure of ureter to 1500 rep In 10 animals, 1500 rep was administered to the ureter and subsequent changes followed by intravenous pyelography Figure 1, *B* shows the results observed The diminishing hydronephrotic changes seen at 6–8 weeks after irradiation with 700 rep are not present Instead, a sustained, uniform degree of hydronephrosis persists until 12 weeks, after which a beginning decrease is noted

Examination of rat kidneys at varying intervals after irradiation demonstrated changes compatible with those noted by intravenous pyelography Macroscopically, the renal pelvis and ureter proximal to the scarred area were dis-

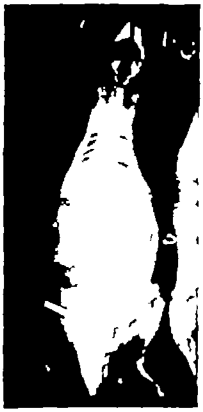

FIG 2 Intravenous pyelogram of rat seven weeks after irradiation of ureter (700 rep)

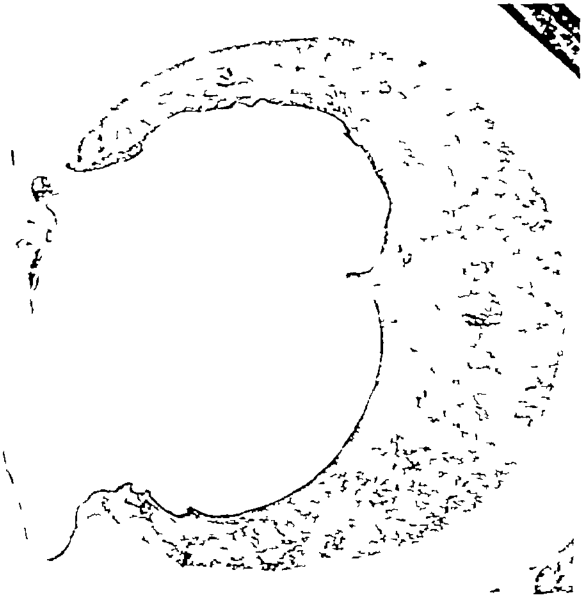

FIG 3 Rat kidney one month after direct irradiation of ureter with 1500 rep Note distended pelvis and dilated tubules X7

tended The kidneys appeared larger and darker in color than normal Microscopically, varying degrees of tubular dilatation were present Figure 3 shows the hydronephrotic changes observed one month after irradiation with 1500 rep This animal had grade 4 pyelographic changes prior to sacrifice

DISCUSSION

Complete ureteral ligation has been used in the experimental study of hydronephrosis,[2] hypertension[3] and pyelonephritis[1] This procedure, however, with its attendant rapid destruction of tissue and loss of function, does not permit prolonged observation of the experimental situation In a model with partial ureteral obstruction such study would be possible in a functioning kidney

Beta irradiation was used in these experiments to produce ureteral trauma with resultant scarring and partial obstruction because of availability, ease of handling and limited depth of penetration The effects of beta irradiation observed are similar to those noted by other workers employing different experimental models Wirth and Raper[4] used P^{32} to evaluate the response of human skin to beta irradiation Employing four doses (635, 813, 1000, and 1180 rep), they described two distinct time reactions of erythema, a primary reaction noted within six hours and persisting two to four days (when the higher doses were used), followed by tanning, and a secondary erythema becoming apparent 19 to 21 days later, followed by additional tanning They also noted that with higher doses (1000 and 1180 rep) the primary and secondary reactions persisted for a longer time In the present experiments, a primary maximum degree of hydronephrosis was noted two to four weeks after irradiation with 700 rep followed by a less marked secondary response at 10 to 14 weeks In rats irradiated with 1500 rep the persistent duration of hydronephrosis represents the more prolonged response to higher doses of irradiation This response was beginning to subside during the end of the observation period but possibly continued study might have revealed a delayed secondary response

The ability to produce ureteral obstruction with a dose of 700 rep but not with 300 rep is compatible with dose-effect relationships described by other investigators Snider and Raper,[5] using histopathologic examination of mouse tissue after external beta irradiation (5000 and 2500 rep) noted that damage is always greater after the higher dose No changes were found characteristic of one dose and not the other, differences were only a matter of degree Further evidence of a relationship between dose and effect is mentioned by McDonald and Wilder[6] Using a strontium^{90} applicator (tracerlab) as a source of beta particles, they were able to demonstrate gross inhibition of corneal wound

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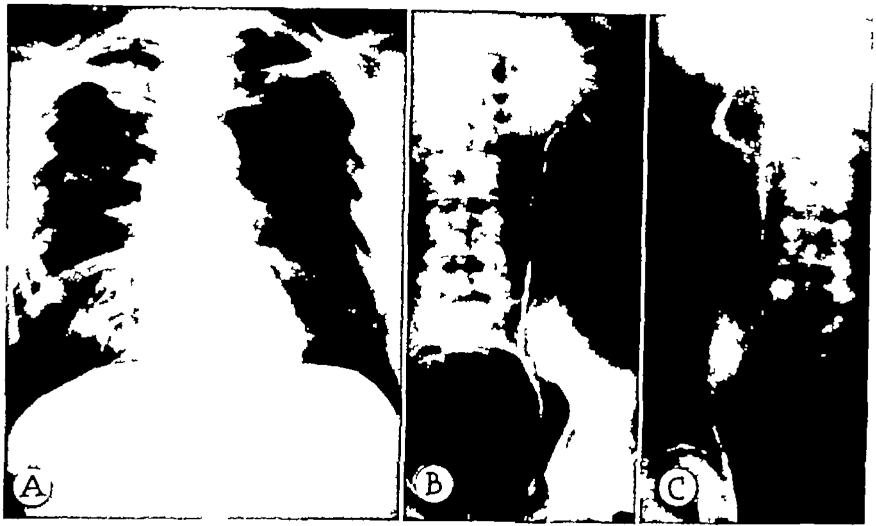

Fig 1 A, density in region of apex of right lung clearly visible B, left retrograde pyelogram C, right retrograde pyelogram

of assurance that therapy was not being withheld from an obscure inflammatory lesion, bilateral renal exposure via the vertical approach of Simon was undertaken Both kidneys were enlarged, pale and turgid Tissue removed at biopsy was grossly seemingly caseous The pathologist's report identified the material from each kidney as undifferentiated carcinoma

Progressive general physical deterioration continued and the patient expired 29 days following admission to the hospital

Postmortem examination revealed widespread carcinomatous involvement of the liver, adrenals, and periaortic structures, as well as extensive infiltration of both kidneys Four divergent areas of pulmonary metastasis were noted The sequence of events was postulated as a migration of right renal pelvic squamous cell carcinoma across the midline and into the hilar region of the left kidney From that point a browsing infiltration of each renal parenchyma subsequently prevailed, in addition to involvement of surrounding structures Much of the tumor tissue both in the kidneys and in other areas was of undifferentiated nature but many areas of true squamous cell carcinoma were visible (fig 2)

In reviewing the ten prior reported instances of bilateral renal carcinoma the onset of overt symptoms and signs in persons with so far advanced bilateral renal disease is insidiously unremarkable and parallel arcanely to the clinical picture in our patient Approximately 40 per cent of the reported cases evidenced severely depleted renal function and frequently a preterminal state yet decidedly undramatic urologic prodromata to signify so severe a carcinomatous invasion

The literature reveals that since the first reported case by Chute in 1910, a 62-year-old male patient in whom widespread metastasis was present at the time of diagnosis, each subsequent patient has been of the male sex and all between the fourth and sixth decades The majority of patients were brought to urologic surveillance because of hematuria and the discovery of a flank mass In our

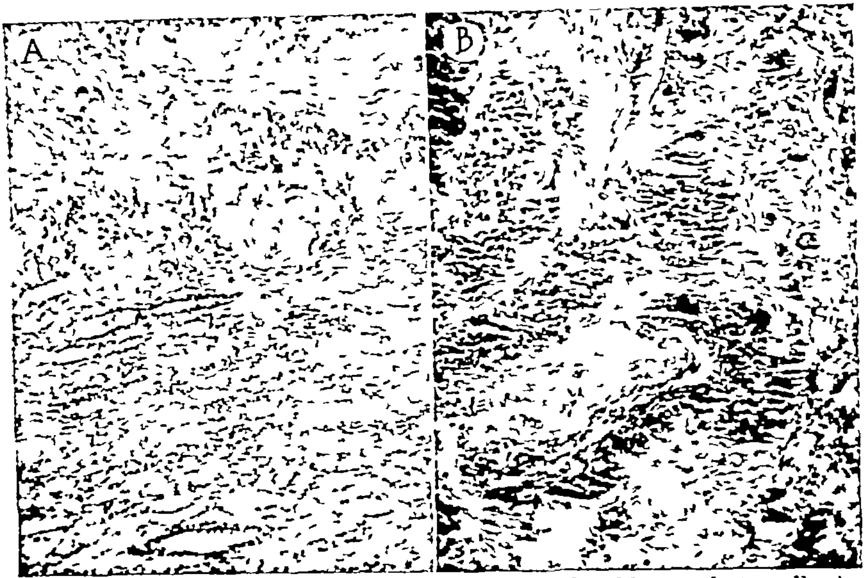

FIG 2 Sections of renal parenchyma almost totally replaced by neoplastic cells Areas of squamous cell carcinoma visible amid undifferentiated carcinoma

patient the mode of the bilateral renal involvement was apparently by extension whereas in previous instances, the tumors with one exception being hypernephroid, blood and lymph borne metastasis rather than infiltration of contiguous structures had been broached as the etiology for the bilateral occurrence Undoubtedly the possibility of simultaneous and separate genesis of renal adenocarcinoma exists and in certain of the reported instances seems probable

Urographic findings in this patient seemingly were sufficiently bizarre to warrant entertaining the possibility of an inflammatory or granulomatous lesion, in several of the previous bilateral adenocarcinomas a diagnosis of polycystic disease had been thought warranted Obviously the rarity of simultaneous bilateral neoplasm is productive of a certain hesitancy in proposing such a consideration

Seemingly a morbid outlook must be maintained in regard to the salvage of patients with bilateral renal carcinomas despite the lengthy survivals which have occasionally been seen in bilateral Wilms' tumor subsequent to unilateral nephrectomy and irradiation The profound renal functional deterioration and advanced stage of neoplastic infiltration which have been evident in most of the reported instances of bilateral tumors in adults would seem to preclude surgical extirpative measures The notorious lack of response to irradiation of the preponderant number of adenocarcinomas and more especially of the urothelial carcinomas would ostensibly obviate consideration of this form of therapy The possibility that the nitrogen mustard compounds could be employed advantageously for palliative purposes exists, and consideration would have been given to their utilization here had not the general physical deterioration of the patient progressed so rapidly

SUMMARY

The occurrence of bilateral, simultaneous squamous cell carcinoma of the kidneys in a 52-year-old man is described in respect to the clinical and pathological picture presented This is apparently the first annotation of bilateral squamous cell carcinoma of the kidneys

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RETROPERITONEAL HEMANGIOMA

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Retroperitoneal hemangiomas are rare lesions They arise from blood vessels The neoplasm affects only one segment of a vessel, from which buds of endothelium grow out and from new vessels in a closed territory (Ribbert)

In reviewing the literature, such tumors in the retroperitoneal space in close association with the kidney and ureter have been reported only by Hilse who described a recurrent retroperitoneal lipoma with areas of cavernous hemangioma Harris has reported a large hemangioma which was perirenal and was mistaken for a kidney Millman described a caverous hemangioma lying on the right ileopsoas muscle and it was removed surgically The authors wish to report an additional case of hemangioma, in a man aged 58, which was removed surgically A previous study of primary retroperitoneal tumors reported by the senior author revealed no tumors of this cell type

CASE REPORT

A white man aged 58 (Mr P D, Unit No 466008) was admitted to the urological service of the New Haven Hospital on April 8, 1957 Two months previously the patient had noted the onset of painless intermittent rectal bleeding Sigmoidoscopy revealed the presence of a rectal polyp Barium enema revealed a well-circumscribed mass in the left upper quadrant, displacing the upper portion of the descending colon anteromedially (fig 1, *B*) The rectal polyp was removed at another hospital, and the patient was referred to New Haven for evaluation of the mass The patient reported excellent health for more than 25 years He denied any history of abdominal pain, weight loss, anorexia, change in bowel habits, hematuria, frequency, or any other urinary symptoms He had been hospitalized only once, 39 years previously, for a tonsillectomy His review of systems was entirely negative except for a chronic nonproductive cough associated with excessive smoking

Physical examination revealed a well-developed, rather obese man who appeared to be in good health His chest was hyperresonant to percussion and there were scattered inspiratory rhonchi over both lung fields The abdomen was obese, but deep palpation high in the left upper quadrant revealed a suggestion of a smooth, slightly tender mass The remainder of the physical examination was negative Admission hemoglobin 16 2 gm per cent, white blood cells 9,800 per c mm, with a normal differential The urinalysis was normal The serum nonprotein nitrogen was 39 mg per cent, and a two hour phenolsulfonphthalein excretion was 40 per cent Upper gastrointestinal series revealed no gastric or small bowel deformity Intravenous urography was deferred because of marked conjunctival reaction to the test that was made Cystoscopic examination

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showed no white cells or red blood cells The urine from the left kidney was normal A left retrograde pyelogram revealed satisfactory visualization of the calyces, pelvis, and ureter, all of which appeared normal in configuration Overlying the lateral border of the left kidney there was a well-defined area of increased density with sharply defined peripheral borders (fig 1, *A*) The oblique view revealed the mass to be anterior to the upper pole It was thought to represent an intra-abdominal cyst of mesenteric origin The differential diagnosis preoperatively included 1) renal cyst, 2) retroperitoneal tumor, 3) kidney tumor, and 4) mesenteric cyst

On April 10, 1957, the left flank was explored through a left transverse subcostal incision Reflecting the peritoneum medially, the kidney was mobilized easily by blunt dissection, and was found to be entirely normal Further exploration external to Gerota's fascia revealed a moderately firm tumor the size of a large orange, located anteriorly to the upper pole of the left kidney It appeared well encapsulated, highly vascular, and was entirely separate from the kidney and peritoneum The tumor was dissected free easily, and removed There was no demonstrable regional or lymphatic involvement The space was drained with a Penrose drain The patient's postoperative course was complicated by development of pulmonary atelectasis and pneumonitis Early congestive failure developed, and the patient was hypotensive for the first 48 hours He responded to appropriate antibiotics, endotracheal suction, and digitalization, and was discharged in excellent condition on the fifteenth day after the operation

The pathology report of the tumor (fig 2) was as follows "A 155 gram roughly ovoid, 7 cm well-circumscribed mass is received A moderate amount of adipose tissue is attached to a thin gray capsule The external surface is smooth with the exception of a 5-6 cm small ovoid projection consisting of tissue similar to the main mass On section the tissue is moderately soft, homogeneous, deep

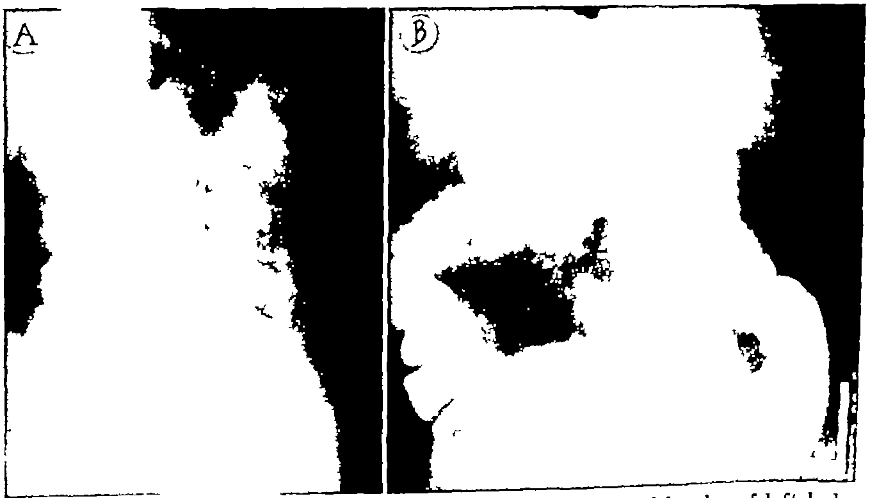

FIG 1 *A*, left retrograde pyelogram shows mass overlying lateral border of left kidney *B*, barium enema reveals anteromedial displacement of upper portion of descending colon by retroperitoneal mass

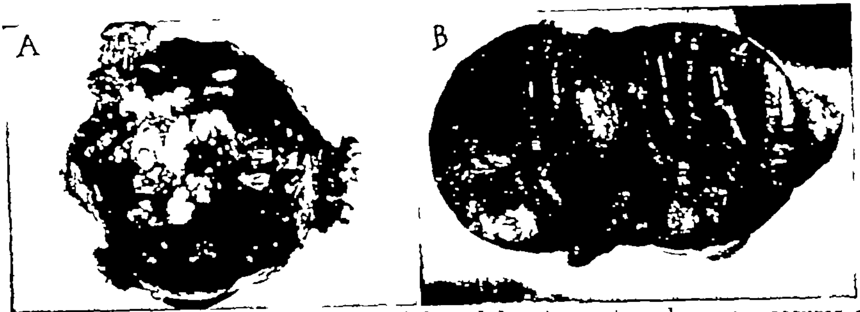

Fig 2 *A*, operative specimen removed from left retroperitoneal space measures approximately 7 cm in diameter *B*, cross section of operative specimen which is well encapsulated

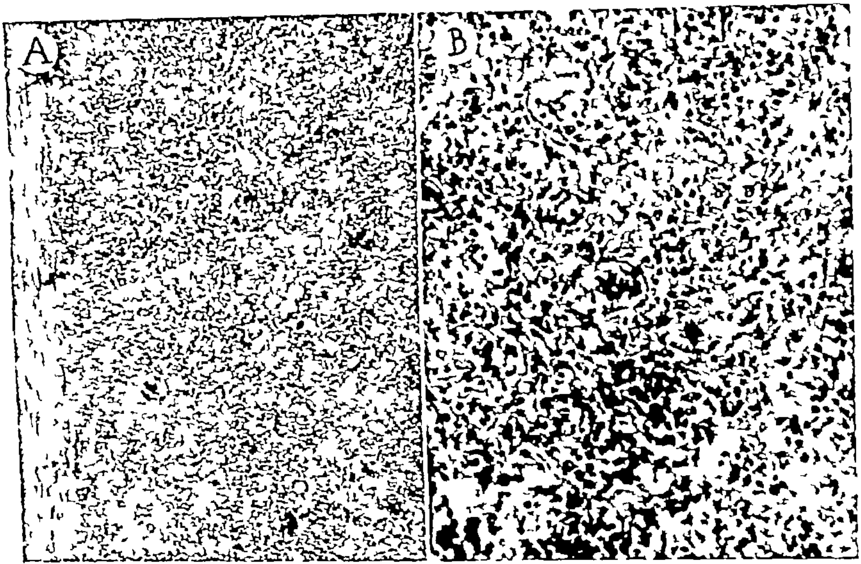

Fig 3 *A*, note dense capsule overlying angiomatous parenchyma × 55 *B*, note detailed structure of tumor, innumerable thin walled lumina and heavy lymphocytic infiltrate

red, and bulges from the cut surface " The microscopic sections (fig 3) show a capsule composed of masses of endothelial cells in which are embedded innumerable capillary lumina These lumina are irregular, and are formed by a single layer of endothelial cells There is a thin stroma containing irregular cells with a large pale nuclei, and poorly defined eosinophilic cytoplasm Scattered throughout the stroma there are many well-defined foci of lymphocytes with occasional plasma cells and eosinophils Pathological diagnosis "Retroperitoneal hemangioma with lymphoid stroma The hemangioma is of capillary type, and since no mitosis is evident, it is doubtful that it is malignant "

COMMENT

A hemangioma is a formation of blood vessels of which two principal types are encountered, the capillary and the cavernous The capillary angioma consists of a network of capillaries filled with blood The neoplasm affects only one segment of a vessel, from which buds of endothelium grow out and form new vessels in a more or less closed territory, without involvement of surrounding vessels (Ribbert) Where the tumor forms a new lobule, or invades fat or other tissue, it is not by extension of the tumor process to the healthy vessels of the new area, but by *projection of new vessels of the surrounding area*

The histogenesis of the hemangioma is obscure In the development of the adult circulatory system, there are formed certain anomalous vascular segments which do not fit into the adult system, and which retain certain embryonal characteristics It is from these vascular segments that capillary tumors appear to arise (Ewing) Other significant factors in the formation of angiomata include the effect of local mechanical irritation or abnormal pressure during the development of the vascular system (Ewing, Stout)

SUMMARY

A case report is made of a retroperitoneal capillary hemangioma removed from an asymptomatic 58-year-old white man This represents the fourth tumor of its type to be recorded in the literature to date

A brief review of the pathology and histogenesis of angioma is made

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TRANSITION OF CYSTITIS GLANDULARIS TO PRIMARY ADENOCARCINOMA OF THE BLADDER

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The manifestations of the forms of proliferative cystitis, particularly cystitis glandularis and cystitis cystica, are well known and are recognized as difficult clinical problems to evaluate and treat Mucus secreting adenocarcinoma arising primarily in the bladder is not commonly seen, but it is not a rare vesical tumor That these lesions are closely related is generally agreed, and the fact that cystitis cystica and cystitis glandularis are pre-malignant lesions has been postulated The demonstration of a direct transition and progression of a case of cystitis glandularis to adenocarcinoma should lend emphasis to the consideration of the malignant potentialities in the clinical management of these forms of cystitis

THEORIES OF PATHOGENESIS

Cystitis glandularis and primary mucus adenocarcinoma of the bladder are closely related lesions[1-15] The similarity of accepted theories of etiology as well as the high incidence of the co-existence of these lesions is evidence of this relationship "Embryonic rests," originating in the urachus or as persistent inclusions of intestinal epithelium misplaced in the process of the division of the rectum from the urogenital sinus, may manifest themselves as areas of cystitis

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glandularis or glandular carcinoma[3, 9, 16, 17] The number of cases that have been reported is not many, but it must be accepted that these lesions may arise on this basis Foot[9] believes that embryonic rests are responsible for all glandular elements found in the fundus of the bladder Primary adenocarcinoma arising in the vesical end of the urachus is well recognized, and the opinion that all primary adenocarcinoma arising in the fundus of the bladder is of urachal origin is frequently documented

It has been reported by some observers that a few glands may occur under normal circumstances in the base and trigonal area of the bladder, and it is on this fact that the anatomical theory of the origin of these lesions is based Emmett and McDonald[3] described five of nine cases of cystitis glandularis which they felt originated in subtrigonal glands They also stated that these glands may give rise to adenocarcinoma Lowry and associates[18] reported three cases demonstrating proliferative cystitis of a glandular type arising from glands of Albarran

The marked ability of transitional epithelium to undergo metaplasia is one of its characteristics, and it is on this basis that the majority of critical opinion believes the etiology of cystitis glandularis, as well as the other forms of proliferative cystitis, and primary adenocarcinoma of the bladder may be best explained[1, 2, 4, 6, 10, 13, 14, 18, 19] With the majority of the vesical epithelium being of entodermal origin, it is theorized that the transitional epithelium retains a tendency, under certain indefinite and incompletely defined forms of stimulation, to form glandular epithelium Beginning with the transitional epithelial unit of metaplasia, the cell nest of von Brunn, the potentialities of change to a glandular type epithelium and thence to a mucus adenocarcinoma have been repeatedly described

COMMENT

The observations of others as well as the pathological studies of the case herein reported lead us to believe that cystitis glandularis is and should be identified as a pre-malignant lesion As Craig[14] has stated, "proof of the relationship of these lesions to adenocarcinoma depends largely on presumptive evidence " However, this evidence is quite convincing even if based only on the high incidence of their reported coexistence

In discussing the differential diagnosis of a primary from a metastatic adenocarcinoma of the bladder, Wheeler and Hill[5] stated that one of the criteria for a diagnosis of primary adenocarcinoma is the coexistence of cystitis glandularis Mostofi,[2] rejecting all theories of origin of adenocarcinoma of the bladder other than that of a direct and progressive metaplasia from transitional epithelium,

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states that to call a tumor a primary vesical carcinoma, Brunn's nests, glandular and mucus metaplasia as well as polypoid epithelial projections must be present. The evidence of these reports as well as that of the case herein described suggests that the observations of the coexistence of adenocarcinoma and cystitis glandularis are important but further and more important that cystitis glandularis may be only the mid-point of a progressive transition in the metaplasia of transitional epithelium to adenocarcinoma.

Craig[14] stated that "it would be difficult to recognize the condition (i.e. cystitis glandularis) in the inflammatory stage during life and follow it over a period of years to the development of malignancy." Patch and Rhea[8] in 1935, stated that it must be admitted that the progressive changes in cystitis glandularis leading to adenocarcinoma have not been demonstrated. Coppridge, Roberts and Culp[16] in 1951 although agreeing that it does occur stated that "adenocarcinoma has never been observed to occur from cystitis glandularis." We have been unable to find any report in which the transition of cystitis glandularis to adenocarcinoma has actually been demonstrated in a given patient.

CASE REPORT

The following case demonstrated this transition from cystitis glandularis to primary mucus adenocarcinoma.

M. A. (H. H. 54260) a 41-year-old white woman was admitted to Hahnemann Hospital on April 12, 1951 with the chief complaint of an incisional hernia, dysuria, and cloudy urine. The urinary symptoms dated back eight years to

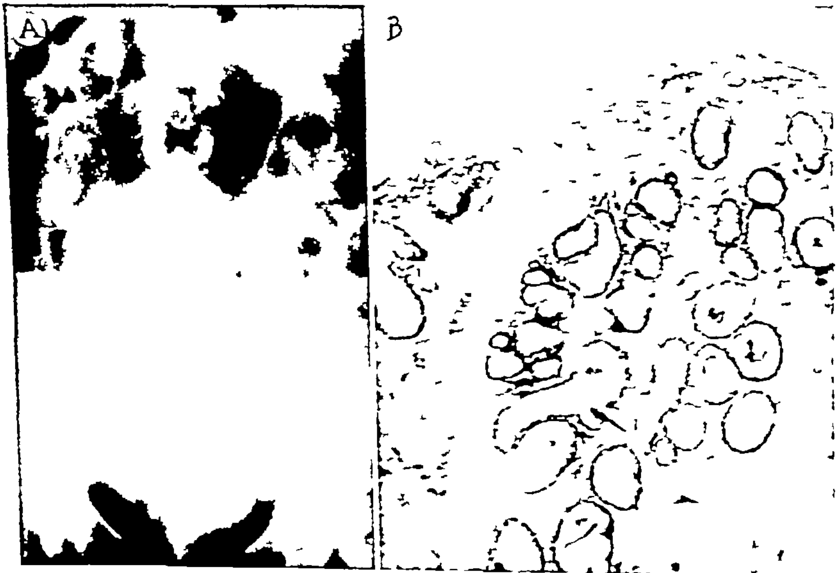

Fig. 1. A, intravenous urogram shows normal upper urinary tract with filling defect in right lateral wall of bladder. B, section of bladder mucosa shows typical mucus glands (gastrointestinal type) seen in cystitis glandularis.

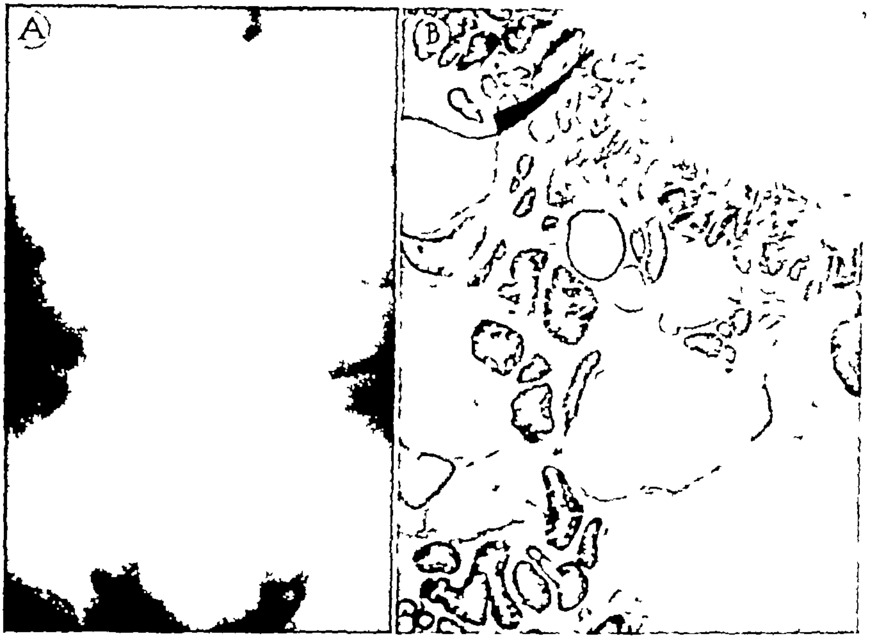

FIG 2 *A*, intravenous urogram again shows defect in right lateral wall of bladder Shadow over bladder region is wire mesh used in repairing incisional hernia *B*, section of bladder shows typical cystic glands In addition, however, there are atypical glands nestled between cystic glands, characterized by hyperchromatism, hyperplasia and invasion of muscle wall

their first appearance following an abdominal operation of an indefinite nature done for a benign gynecological complaint In 1949 dilatation and curettage had been done, the specimen was negative for malignancy Dysuria recurred and had been present for two months prior to the present admission There was no history of hematuria

Physical examination showed a very obese white woman with an incisional hernia in the midline of her lower abdomen, first degree cystocele, two plus pedal and pre-tibial edema The urine showed many mucus shreds, 30 to 40 red blood cells per high power field, and was loaded with white blood cells Aerobacter aerogenes and coliform bacilli were cultured An intravenous urogram revealed good bilateral function with a morphologically normal upper urinary tract There was a large filling defect in the right side of the bladder (fig 1, 4)

Cystoscopy revealed a large, broad base, somewhat elevated tumor mass involving most of the right lateral wall of the bladder The upper portion of the tumor was irregular, the lower part smooth Biopsies taken from the lower and middle areas of the tumor revealed ' polypoid masses lined by adenomatous glands which were mucus secreting in type Diagnosis cystitis glandularis (aberrant gastrointestinal tissue) "

Cystoscopy was repeated six days later and it was noted that the tumor appeared infiltrating Another biopsy was again reported to be cystitis glandularis Gastrointestinal studies were negative except for multiple small diverticula of the upper sigmoid

At operation the bladder was opened through a suprapubic incision, and the major portion of the tumor was removed by loop resection and the base fulgurated Pathological examination revealed "nests of adenomatous glands lined by tall columnar and mucus secreting epithelium An occasional nest of transitional epithelium is noted Again the possibility of gastrointestinal malignancy cannot be excluded Diagnosis cystitis glandularis (fig 1, *B*) "

During the six months following her discharge from the hospital, the clinical picture was that of marked frequency, urgency, suprapubic pain, hematuria and cloudy urine with large amounts of mucus Resistant B proteus was repeatedly cultured The patient was hospitalized for cystoscopy under anesthesia and a generalized hyperemia with an elevated area, cystic in appearance, and irregular in form, 2 to 3 cm above the right ureteral orifice, was described An interval cystoscopy a month prior to this admission had revealed mucoid plaques and areas of extreme hyperemia limited to the right lateral wall Biopsy and cystoscopic treatment were advised, but the patient left the hospital

The patient returned to the clinic 22 months later complaining of frequency, nocturia and burning on voiding During the interval the incisional hernia had been corrected at another hospital using a wire mesh repair Her urine contained mucus shreds Cystoscopy revealed a red, velvety mucosa with a mucoid exudate No mention of tumor was made

She was not seen for another eight months at which time she was admitted to the hospital because of severe pain in her right hip Bladder symptoms were not prominent Bone x-rays were negative An intravenous urogram revealed a normal upper tract and again showed a filling defect on the right side of the

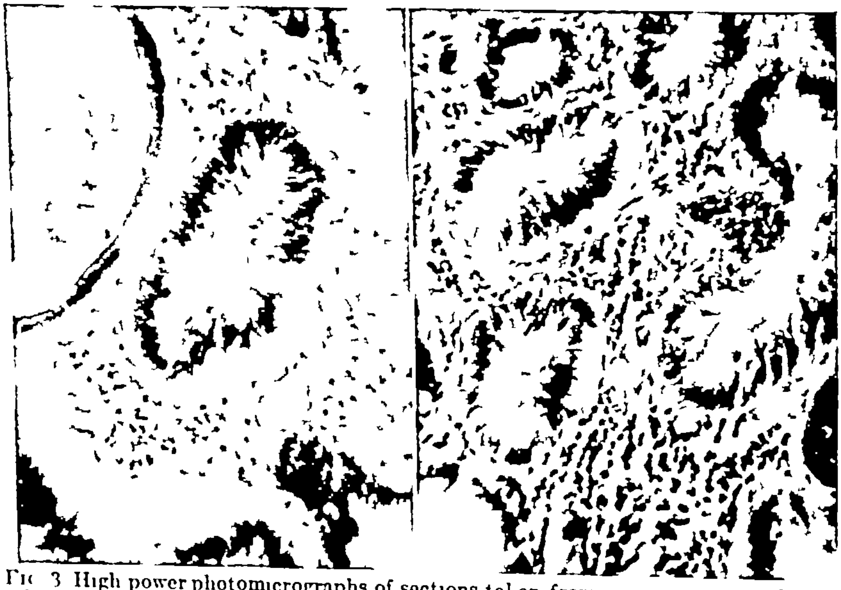

Fig 3 High power photomicrographs of sections taken from specimen removed by subtotal cystectomy reveal hyperchromatism of nuclei, loss of nuclear polarity, and occasional mitotic figure and invasion Stroma is characterized by diffuse mononuclear cell infiltrate

bladder (fig 2, *A*) B proteus and coliform organisms sensitive to streptomycin were cultured from the urine *Cystoscopy revealed a papillary tumor on the* right lateral wall with hyperemia of the bladder base The clinical impression was transitional cell carcinoma Another biopsy was reported "mucosa entirely replaced by mucinous glandular formations which invaginate up to the submucosa The interglandular stroma shows loose fibrous connective tissue with diffuse lymphocytic infiltration Diagnosis cystitis glandularis" (fig 2, *B*) The patient was discharged two days later

She returned intermittently during the next seven months during which time her bladder symptoms *remained unchanged A culture during this period* revealed paracolon and coliform bacilli

The patient was then not seen until her return to the clinic in May 1956, five years and one month from the time of the original biopsy and diagnosis of cystitis glandularis Her complaints were frequency, nocturia and, now, stress incontinence Cystoscopy revealed an irregular, non-ulcerated, hyperemic tumor involving most of the right lateral wall The clinical impression was again that of carcinoma and she was admitted to the hospital, her fourth hospital admission *Physical examination revealed a well preserved, extremely obese white woman* Routine blood studies were within normal limits An intravenous urogram again showed the deformity of the right wall of the bladder Repeat studies of the lower bowel were unchanged from previous studies The chest x-ray was negative Her urine showed many red and white blood cells and culture yielded coliform bacilli

Transurethral biopsy of the right lateral wall lesion was reported by the pathologist that "*the tissue is composed of mucus secreting glands in a loose granulation tissue type of stroma Lymphocytes infiltrate diffusely* Many areas of the glands show loss of polarity and hyperchromatism of nuclei with occasional mitoses Comparison with previous biopsies shows that this lesion has undergone malignant change and should be thought of as a low-grade adenocarcinoma primary in the bladder Diagnosis "Adenocarcinoma of the urinary bladder, low-grade "

A subtotal cystectomy was performed A large papillary tumor which involved most of the right lateral wall was removed with what was felt to be an adequate margin of normal bladder wall There was no evidence of local or distant extension of the lesion The postoperative course was prolonged by persistent drainage from her suprapubic fistula She was discharged on the thirty-fourth postoperative day

The pathology report stated that, "The major specimen reveals a glandular tumor composed of well differentiated mucus producing glands These grow up from the surface in a polypoid tumor, but some glands are invasive and extend down to the muscle Diagnosis Adenocarcinoma of the urinary bladder" (fig 3)

On her return to the clinic two weeks after discharge she was voiding four times during the day and twice at night without pain

DISCUSSION

In 1951 the lesion was unequivocably cystitis glandularis (fig 1, *B*) After three years of chronic infection the patient returned with a lesion in the same area of the bladder, which on biopsy was again diagnosed as cystitis glandularis, but in reviewing the slides we find beginning carcinomatous change with piling up of nuclei and loss of polarity (fig 2, *B*) Then after two additional years of chronic infection, the patient was seen with the same lesion which had progressed to an early infiltrating mucus adenocarcinoma with areas of loss of polarity and hyperchromatism of the nuclei with mitoses (fig 3) In a period of five years unequivocal cystitis glandularis had progressed to unequivocal mucus adenocarcinoma with beginning malignant change in the third year

The role of chronic infection in the production of these lesions has been stressed by many authors[1-5, 7, 14, 20] There is little doubt that it was a factor in this case Perhaps the progression to anaplasia would not have occurred without the inflammatory stimulation

Sauer and Blick[21] followed five cases, in which there was no infection initially or it had been eradicated, for periods of one to six years, and reported no evidence of malignant degeneration Their observations were made on cystoscopic evidence No mention was made of repeat biopsy We shall follow our case with interest to see if her bladder epithelium will remain normal following eradication of infection If her infection persists, will cystitis glandularis recur and progress to malignancy, or will she have a recurrence of adenocarcinoma without glandular metaplasia?

The clinical and pathological diagnosis of an early primary adenocarcinoma and its differential diagnosis from that of cystitis glandularis is not always easy A resistant, symptomatic infection is usually present That a biopsy or several biopsies would be truly representative of the areas showing the greatest degree of anaplasia will always be a doubtful fact Adequate study and interpretation of the biopsy submitted are subsequent problems which need further elaboration

Having arrived at the diagnosis of early primary adenocarcinoma and having ruled out a primary lesions elsewhere, the lesion should be treated as any other carcinoma of the bladder

If the diagnosis be cystitis glandularis, the lesion should be adequately resected and its base fulgurated The patient's infections should be vigorously treated and eradicated Failure to respond to treatment should alert the clinician to the necessity of close followup, repeated biopsies, and constant attention to the possibility that he is dealing with a potentially malignant lesion

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SUMMARY

There is a close relationship between cystitis glandularis, one of the common forms of proliferative cystitis, and primary mucus secreting adenocarcinoma of the bladder

This relationship has been emphasized in the past but only on presumptive evidence based on the high incidence of the coexistence of these lesions and the similarities of theories of pathogenesis The embryonic rest theory, the anatomical theory, and the theory of the metaplastic transposition of transitional epithelium to a glandular type epithelium and adenocarcinoma are noted The latter is the most widely accepted

A patient with cystitis glandularis was followed carefully over a period of five and a half years and a definite transposition to a mucus secreting adenocarcinoma was demonstrated To the authors' knowledge, this is the first report in which this change was actually observed and demonstrated in a given case

This report adds to the evidence that cystitis glandularis, as well as the other forms of proliferative cystitis, is a premalignant lesion of the bladder, and it is urged that this fact be kept in mind in the clinical management of these forms of cystitis

The authors wish to thank Dr F Mostofi and his staff at the Armed Forces Institute of Pathology for reviewing the slides in this case

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TUMORS OF THE BLADDER IN INFANTS: A CASE REPORT OF A BENIGN TUMOR AND A REVIEW OF THE LITERATURE

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Malignant tumors of the bladder in infants are rare and benign tumors are even more rare. Wells found no bladder tumors in 3011 autopsies in newborn infants. Potter reports that in 2000 autopsies in infants under one year of age only one neurinoma with widespread neurofibromatosis and ganglioneuroma was encountered.

Thirty cases of malignant tumors of the bladder in infants have been reported (table 1). The malignant bladder tumors most often encountered are embryonal myosarcomas, so-called sarcoma botryoides, and myxosarcomas. We have found only eleven reported cases of benign bladder tumors in infants (Dennis; Green and Ainsworth) (table 2). These were polyps, two hemangiomas, one neurofibroma, one fibroma, one fibromyxoma, one leiomyoma, one myoma, one dermoid tumor, and one with multiple wart-like cysts.

The outlook of malignant tumors of the infant is very somber. None (table 1) are reported to have survived with any therapy other than total cystectomy with or without pelvic exenteration. Radiation therapy does not seem to control the growth or recurrence due to their insensitive nature.

The benign tumors, although less important, may provoke complications by interfering with urinary flow. This would lead to obstruction with ensuing infection or renal insufficiency and irreversible renal damage (Campbell, 1951, 1952; Lowsley and Kirwin; Nelson).

The usual presenting symptoms of infants who have bladder tumors are difficult to evaluate. If carefully observed by their parents, painful urination as well as marked frequency of urination may be elicited in the history. Gross hematuria may occur when the tumor undergoes ulceration. More commonly the child will present a failure of weight gain and loss of appetite with corresponding poor nutrition. In females, a total protrusion of the tumor through the urethra has been reported (Green and Ainsworth; Marshall). When infection has supervened, producing a cysto-pyelonephritis, high fever is the usual presenting complaint.

Examination may reveal little, with the exception of the possibility of demonstrating a palpable tumor mass. Albuminuria out of proportion to the cellular findings, in the absence of other more obvious causes, suggests the possibility of tumor in the genitourinary tract (McQuarrie; Campbell; Nelson). Intravenous or subcutaneous pyelography followed by cystoscopy and biopsy will ascertain the nature, extent and obstructive course of the lesion.

Benign tumors may be treated by local excision by the transurethral or open suprapubic approach. Malignant tumors, however, should be handled by radical

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SUMMARY

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centrifuged urine specimen The infant was admitted to the hospital after being afebrile for two weeks for a urological investigation

The past history as well as the family history was unknown since she was an adopted child The infant was an exceptionally "good natured" child who ate well prior to the present illness However during the weeks before admission, she had refused one meal each day

Physical examination revealed the infant to be chubby, well developed, well proportioned and cheerful Her tonsils were enlarged and reddened Her blood pressure was not elevated in her arm or her leg by the flush technique Her heart and lungs were normal Rectal examination revealed no abnormality Abdominal examination disclosed some resistance noted in the lower abdomen on the right side

A pyelogram obtained by subcutaneous urography showed an ovoid filling defect (fig 1), measuring approximately 1 cm in its greatest dimension at the most inferior portion of the bladder, and there was early dilatation of the lower right ureter Blood urea nitrogen determinations revealed elevated values of 46, 30, and 35 mg per cent Cystoscopic examination revealed a smooth rounded mass about 0 75 cm in size in the trigone of the bladder The right ureteral orifice was edematous, and the left orifice was not visualized Specimens from three different sites of the mass were obtained transurethrally These demonstrated a vascularized, slightly inflamed and edematous fibrous connective tissue and muscle from the bladder A tentative diagnosis of myoma was later confirmed by further study of the entire excised mass (fig 2) Chest and bone survey x-rays showed no metastatic lesions At this time urinalyses revealed no albumin or white blood cells even though no treatment had been given since the previous analysis However, gamma streptococci and Aerobacter aerogenes were cultured, and appropriate antibiotics were prescribed

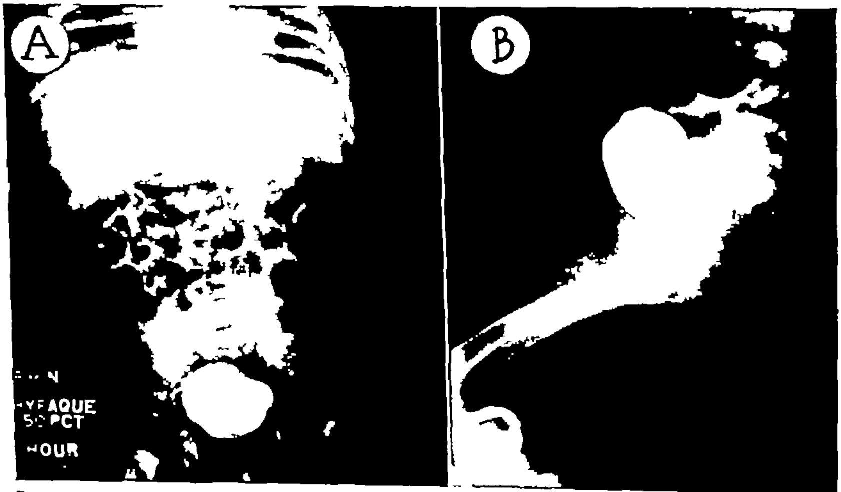

FIG 1 *A*, subcutaneous pyelogram reveals filling defect in bladder and early dilatation of right ureter Renal shadows normal *B*, cystogram with irregularity in posterior portion

TABLE 1 *Malignant tumors of the bladder in infants 1863–1957*

No Cases	Age Range	Type of Tumor	Follow up
18	5 wks to 21 mos	Rhabdomyosarcoma (sarcoma botryoides)	15 died 2 lived (2 yr follow) 1 lived (5 yr follow)
10	4½ mos to 24 mos ±	Myxosarcoma	8 died 2 unknown
1	24 mos ±	Leiomyomyxosarcoma	Died
1	24 mos ±	Unknown	Unknown
Total—30	Mean—18 mos		

TABLE 2 *Benign tumors of the bladder in infants 1860–1957*

No	Age	Sex	Year Reported	Author Reporting	Diagnosis	Follow up
1	2	M	?	Kaufman	Myoma	Died
2	1½	M	1905	Huesler	Fibroma	Died
3	2	M	1860	Forster	Fibromyoma	Died
4	2	M	1940	Bongiorno	Fibromyxoma	Died
5	13 mos	M	1911	Koll	Polyp	Cured
6	1¼	M	1949	Ammoniti	Polyp	Cured
7	Small boy		1951	Higgins, Williams and Nash	Multiple nevi	Recovered
8	Newborn	M	1847	Martini	Dermoid cyst	Died 10 days postoperatively
9	2	M	1937	Rathbun	Hemangioma	Recovered
10	1½	M	1944	Kapur	Capillary hemangioma	No followup
11	1 mo	F	1951	Higgins, Williams and Nash	Neurofibroma	Died 7 days postoperatively
12	5 mos	F	1957	Russell, Lipin and Gaines	Myoma	Recovered

cystectomy, pelvic exenteration, and ureteral diversion Segmental resection or irradiation is of no apparent help in removal of the primary growth or in preventing recurrences (Dean, Slotkin and Davis, Marshall)

CASE REPORT

A five-month-old white female infant was admitted to the pediatric service of the Cedars of Lebanon Hospital on November 26, 1956 There was a history of recurrent high fever up to 105F about every four weeks starting three months prior to admission Each episode lasted three to five days She was treated for tonsillopharyngitis during the first two episodes with antibiotics The urinalysis on two samples immediately after the third episode was reported to show 4 plus and 3 plus albumin, and 2 to 3 white blood cells per high power field in a non-

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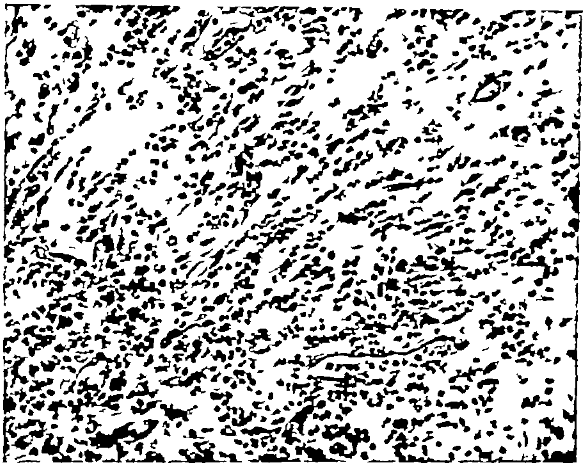

FIG 2 Myoma of bladder

Since the possibility of malignancy was not ruled out by the primary transurethral biopsy, it was decided to remove the tumor suprapubically and perform immediate frozen section In the event that it was malignant, total cystectomy was planned However, biopsy revealed benign tissue throughout the entire mass The base of the area was then fulgurated, and this was deemed adequate therapy The final histological interpretation was that of a benign myoma

Postoperatively, the patient required two transfusions of 75 and 100 cc each, given 24 and 48 hours later at which time her hemoglobin became stabilized Recovery was rapid thereafter, and the patient was discharged ten days postoperatively Followup cystoscopic examinations three and six months later revealed neither recurrence nor episodes of urinary infection

SUMMARY

The brief literature on bladder tumors in infants has been reviewed

Tumors of the bladder in infancy are extremely rare Malignant bladder tumors have been reported in 30 cases and benign tumors in 11 cases

A case report is presented of a benign bladder tumor in a five-month-old infant which was successfully treated with local excision and electrofulguration

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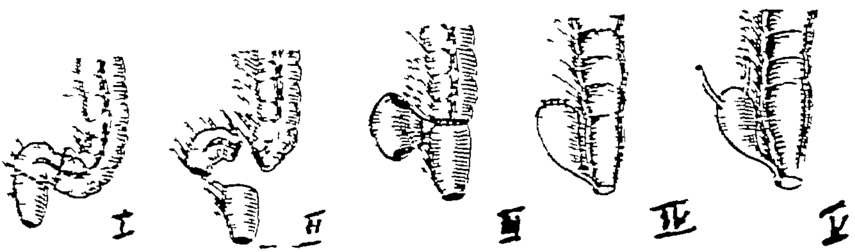

FIG 1

and major labia quite widely at their upper pole The clitoris was lacking The bladder orifice was visible under the pubic region urine flowed freely from it The skin of the thighs the seat and the vulva were inflamed macerated and at places covered with suppurating papulae and crusts The inflamed places were painful

The blood picture and the sedimentation rate were normal

Urinalysis Albumin negative sugar negative specific gravity 1 022 acid reaction, sediment six to eight leukocytes Blood urea 27 mg per cent Intravenous urography and cystography were normal.

The preoperative treatment lasted 5 days The urine was withdrawn through a permanent catheter and the inflamed skin was smeared with zinc paste Four grams of sulfonamides were administered daily to disinfect the intestine. Prior to operation castor oil was administered to clear the intestine, followed by enemas.

The operative method had been first tried on cadavers Our purpose was to make a new bladder out of sigmoid colon and form a tube which would be the urethra of this new bladder The sphincter ani was to close new urethra

To ensure the success of the operation we carried it out in two stages

1) The first step was to make the new bladder and to bring its distal end parallel to the rectum intrasphincterally In a short time it was to be cleaned and its function tested

2) The next step was to implant the ureters into the new bladder

The first stage of the operation was performed on June 1 1956 Posterior medial laparotomy was done under general anesthesia with either The intestines were pushed up to the diaphragm and carefully isolated The plica retrouterine was opened A blunt tunnel was made between the ventral side of the rectum and the dorsal side of the vagina reaching as far as the perineum. A resection was made in the sigmoid section of the large intestine at the point of the greatest curvature The length of the incised fold was about 25 cm. the mesenterium and the arteries were not cut The incised fold was then separated and wrapped up in a gauze compress (fig 1) The passage of the large intestine was restored by joining it end to end The oral end of the incised intestine fold was sutured with double stitches The distal end was so reshaped that after narrowing it down it assumed the form of a pear (fig 1)

Thus shaped, the new bladder was placed in the tunnel made for it Part of the bladder stuck out of the tunnel, in the abdominal cavity and was peritonealized with the peritoneum incised in the region of the plica retrouterine Several

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SUBSTITUTE BLADDER MADE OF SIGMOID COLON

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Diversion of urine into the intestine is not a new phenomenon The British surgeon, John Simon was the first to divert urine into the intestine as early as 1851 The first implantation of ureters disconnected from the bladder was accomplished by T Smith in 1878 and consisted of the anastomosis of the mucous membrane

Diversion of urine into the intestine is indicated in the following cases complete incontinence associated with exstrophy of the bladder, epispadias and hypospadias, inoperative vesicovaginal fistulas, irreparable blockage of the urethra, when the bladder has shrunk to the highest degree in consequence of cancer, or tuberculous or other inflammation of the bladder, in cases of cystectomy or as a palliative measure because of unbearable pain

A difference should be made between methods aimed at diversion of the urine and methods in which continence is not preserved The former presuppose an intact sphincter ani, while the latter are cases of pyelostomy and cystostomy Exstrophy or cancer of the bladder is the most frequent indication for diversion of the urine into the intestine There are two possibilities a) to implant the ureters straight into the intestine and b) to implant the ureters directly into a small separate part of the colon which is to replace the bladder

Until recently it was believed that urine diversion had found its final solution in ureterosigmoidostomy This operation, which has lately been performed more frequently with greater facility and certainty, is nevertheless followed by some delayed and often fatal consequences This has made the surgeons consider the problem of replacing the bladder with a new one, made of the large intestine, part of the skin or folds of the small intestine

We performed cystectomy on three patients who had constant incontinence due to a congenital anomaly of the bladder

CASE REPORTS

Case 1 N Y , 17 years old, a housewife, had exstrophy of the bladder The urine flowed constantly, soiling her body and clothes, causing itching, an unpleasant odor and eczema on the skin around the urinary orifice and the inside of the thighs She had been treated many times, mostly in a conservative manner, without any improvement A year earlier she had undergone an operation, an attempt being made to create an artificial urethra, but the operation was not successful

Diagnostic procedures disclosed light pleural adhesions at the base of the right lung, and a lightly expressed mitral vitium The remaining tests gave normal results The soft tissues in the pubic region were divided by a wide furrow which continued downward to the outer genitalia and separated the minor

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by the threads attached to it, the threads were clamped with forceps and drawn out The end of the new urethra was sutured to the skin incision with single catgut stitches which were reinforced at places with single silk sutures A rubber catheter was placed in the ureteral orifice for a few days

The postoperative period was comparatively smooth Moderate doses of antibiotics and cardiac preparations were prescribed At the end of the first week the cavity of the new bladder was rinsed out with physiological serum to test its future function The patient managed to hold the injected liquid several hours The emptying of the bladder was preceded by calls for defecation The capacity of the new bladder was 500 cc

The second operation was performed on June 29, 1956 at the end of the fourth week Laparotomy was repeated under anesthesia with ether New adhesions were discovered around the organs in the small pubis as a result of the operation The natural bladder was opened Thin catheters were placed in the ureters until they were disconnected Circular incisions were made on the bladder membrane around the ostia which were separated, together with the ureters and the adjacent tissue The latter were connected by means of terminolateral anastomosis with silk stitches in two stages A rubber catheter was placed in the urethra to draw off the urine during the first week

In the postoperative period the patient was subjected to intensified therapy, antibiotics and diuretic preparations were prescribed No opiates were administered The urine was voided normally, but up to the end of the first week it was mixed with large amounts of mucus The tests showed albumin, mucus and bacteria The reaction was alkaline Six days after the operation the patient was able to hold her urine for short intervals of one to two hours For the first

FIG 4 Case 2 Exstrophy of bladder

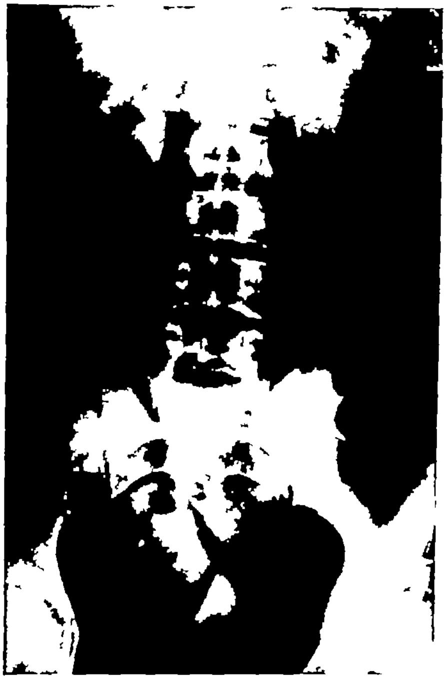

FIG 2 Case 1 Intravenous pyelography 10 months after operation

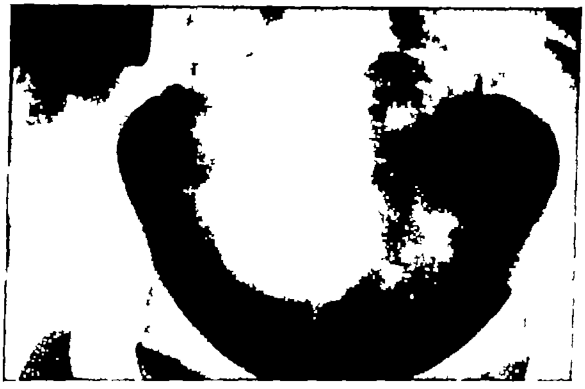

FIG 3 Case 1 Ten months after operation the bladder was pear shaped

thick threads were tied to the end of the new urethra and left hanging They were to be used later in pulling the urethra in the perineal region Antibiotics were placed in the abdomen and the various layers were closed in succession

The patient was placed in a gynecological position for the rest of the operation An arc-shaped incision was made in the perineum, nearer to the anus and the rectal mucosa was separated to about 3 cm behind the sphincter ani Under the control of the finger the rectal ventral wall was incised sideways about 2 cm In this way a connection was established with the lower end of the tunnel where the distal part of the bladder rested Then the new urethra was pulled out easily by the threads attached to it, the threads were clamped with forceps and drawn out The end of the new urethra was sutured to the skin incision with single catgut stitches which were reinforced at places with single silk sutures A rubber catheter was placed in the ureteral orifice for a few days

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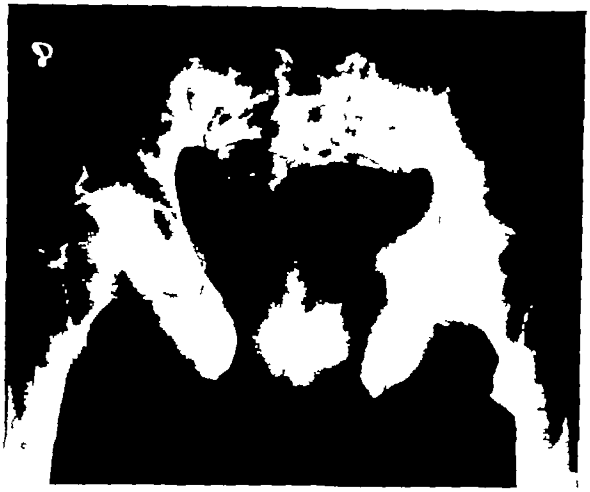

FIG 5 Case 2 Anomaly of pelvic bone

time she felt a call to urinate, which she had never experienced previously She urinated at increasingly longer intervals, five to six times in 24 hours after the end of the second week She did not have to get up at night On the sixteenth day after the operation the urine had an acid reaction, the albumin disappeared, the sediment contained 7–8 leukocytes Culture yielded Escherichia coli The urea content was normal throughout the entire operative period The condition of the patient was grave until the end of the first week She complained of sharp pains in the back and in the lower abdomen, general weakness and inertia Her temperature ranged between 38–39C for a week In the second week the patient recuperated very quickly and 19 days after the second operation she was allowed to leave the hospital completely recovered

Ten months later examination revealed that the patient's condition was satisfactory She had gained 16 kilograms She urinated 5–6 times in 24 hours and did not have to get up at night The average amount of urine was 200–250 cc The capacity of the bladder was 400 cc without residual urine The blood picture and the sedimentation rate were normal Several tests of the urine showed albumin negative, acid reaction, sugar negative, sediment 3–4 leukocytes and fatty degenerated cells, blood urea 20 mg per cent Intravenous pyelography and ureterography were normal (fig 2) The new bladder had assumed an oval shape (fig 3)

Case 2 M I I , 46 years old, a farmer, had exstrophy of the urinary bladder (figs 4 and 5) The anomaly affected the pubic bones, the symphysis was not closed, there was no navel, the penis was hypotrophied and no urethra was present

The patient was admitted to the hospital on April 9, 1957 with an elevation of temperature Examination showed cystopyelitis and bronchopneumonia of the right lung which extended the preoperative period to 20 days

The first stage of the operation was performed on April 29, 1957 The same operative method was applied as in the first case In the second stage, performed on May 17, the ureters were implanted by cutting them above the bladder, because the mucosa of the latter was hypertrophied and unsuitable for anastomosis The postoperative period proceeded as in the first case The febrile period also lasted about a week Administration of antibiotics was stopped in spite of the high temperature because it was established that the colon bacilli isolated from the urine were resistant to antibiotics and sulfonamides The patient received cylotropin orally with very satisfactory results The temperature dropped the day following administration The urine remained alkaline during the entire period of hospitalization, but the sediment became nearly normal, its rate, however, remained fast Blood urea was normal throughout hospitalization

The wound drained in its lower end up to the third week as a small gauze drainage was placed subcutaneously in place of the extirpated bladder After 25 days, the patient was discharged from hospital completely recovered

In both cases the first stage of the operation was performed in two hours, the second in an hour and a half

Case 3 H I P , 11 years old, was operated on by the same method The anomalies resembled those of our second patient

CONCLUSION

The operation on three patients with incontinence of the urine, in which cystectomy was effected and a new bladder made of the large intestine, gave very good results

The operation should be performed in two stages to avoid operative shock and to obtain better results

The tunnel should be made first, care should be taken not to injure the wall of the rectum, which may result in fistulas

In resection of the intestine, care should be taken not to injure the blood vessels which may lead to necrosis and failure of the whole operation

In transposing the bladder the length of the mesenterium should be sufficient for the perineum to be reached without too much stretching

The separation of the ureters should be done atraumatically, catheters should be placed in them before separation

Anastomosis of the new bladder should be effected terminolaterally to avoid stenosis, the suturing should always be done with silk thread

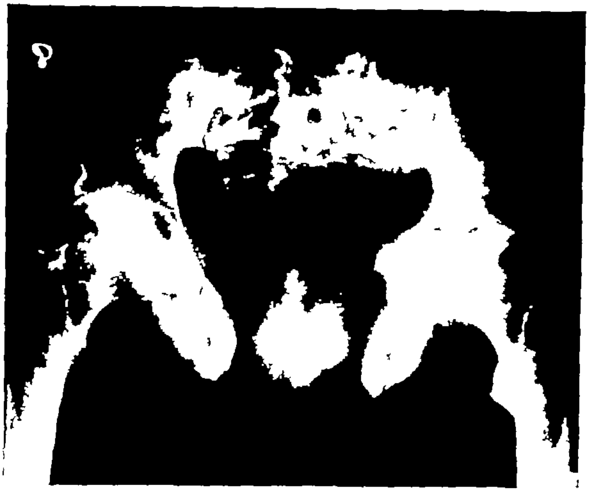

FIG 5 Case 2 Anomaly of pelvic bone

time she felt a call to urinate, which she had never experienced previously She urinated at increasingly longer intervals, five to six times in 24 hours after the end of the second week She did not have to get up at night On the sixteenth day after the operation the urine had an acid reaction, the albumin disappeared, the sediment contained 7–8 leukocytes Culture yielded Escherichia coli The urea content was normal throughout the entire operative period The condition of the patient was grave until the end of the first week She complained of sharp *pains in the back and in the lower abdomen, general weakness and inertia Her* temperature ranged between 38–39C for a week In the second week the patient recuperated very quickly and 19 days after the second operation she was allowed to leave the hospital completely recovered

Ten months later examination revealed that the patient's condition was *satisfactory She had gained 16 kilograms She urinated 5–6 times in 24 hours* and did not have to get up at night The average amount of urine was 200–250 cc The capacity of the bladder was 400 cc without residual urine The blood picture and the sedimentation rate were normal Several tests of the urine showed albumin negative, acid reaction, sugar negative, sediment 3–4 leukocytes and fatty degenerated cells, blood urea 20 mg per cent Intravenous pyelography and ureterography were normal (fig 2) The new bladder had assumed an oval shape (fig 3)

Case 2 M I I, 46 years old, a farmer, had exstrophy of the urinary bladder (figs 4 and 5) The anomaly affected the pubic bones, the symphysis was not closed, there was no navel, the penis was hypotrophied and no urethra was present

The patient was admitted to the hospital on April 9, 1957 with an elevation of temperature Examination showed cystopyelitis and bronchopneumonia of the right lung which extended the preoperative period to 20 days

The first stage of the operation was performed on April 29, 1957 The same operative method was applied as in the first case In the second stage, performed on May 17, the ureters were implanted by cutting them above the bladder, because the mucosa of the latter was hypertrophied and unsuitable for anastomosis The postoperative period proceeded as in the first case The febrile period also lasted about a week Administration of antibiotics was stopped in spite of the high temperature because it was established that the colon bacilli isolated from the urine were resistant to antibiotics and sulfonamides The patient received cylotropin orally with very satisfactory results The temperature dropped the day following administration The urine remained alkaline during the entire period of hospitalization, but the sediment became nearly normal, its rate, however, remained fast Blood urea was normal throughout hospitalization

The wound drained in its lower end up to the third week as a small gauze drainage was placed subcutaneously in place of the extirpated bladder After 25 days, the patient was discharged from hospital completely recovered

In both cases the first stage of the operation was performed in two hours, the second in an hour and a half

Case 3 H I P , 11 years old, was operated on by the same method The anomalies resembled those of our second patient

CONCLUSION

The operation on three patients with incontinence of the urine, in which cystectomy was effected and a new bladder made of the large intestine, gave very good results

The operation should be performed in two stages to avoid operative shock and to obtain better results

The tunnel should be made first, care should be taken not to injure the wall of the rectum, which may result in fistulas

In resection of the intestine, care should be taken not to injure the blood vessels which may lead to necrosis and failure of the whole operation

In transposing the bladder the length of the mesenterium should be sufficient for the perineum to be reached without too much stretching

The separation of the ureters should be done atraumatically, catheters should be placed in them before separation

Anastomosis of the new bladder should be effected terminolaterally to avoid stenosis, the suturing should always be done with silk thread

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COMPLICATIONS INCIDENT TO THE ILEAL CONDUIT

FRANCIS P DE ROSA

Urinary diversion to an isolated segment of terminal ileum has definite advantages over ureterosigmoidostomy and other types of ureterocolic transplants The most important are almost complete absence of hyperchloremic acidosis and reduced incidence of urosepsis

Early complications of this procedure are postoperative paralytic ileus, intestinal obstruction, urinary leakage, pyelonephritis, electrolytic imbalance, azotemia, fecal fistula, wound dehiscence and constriction of the ileal segment due to an inadequate opening in the skin, fascia and peritoneum

Late complications of uretero-ileal anastomosis are progressive unilateral hydronephrosis, pyelonephritis, constricted ileostomy stoma, azotemia, incisional hernia, blistering, dermatitis, and verrucae formation around ileostomy, sensitivity of the skin to paste or bag, technical difficulty with bag or cup, intestinal obstruction, renal or ureteral calculi, acidosis, metastatic or recurrent carcinoma and persistent mucus formation

CASE REPORT

S H , a white man aged 44, was perfectly well until September 1954, when he had an episode of total painless hematuria Cystoscopy revealed several papillary carcinomas of the bladder On March 30, 1955, the patient had an open resection and fulguration of the papillary tumors From July 1955 to January 1956, the patient had three transurethral resections and fulgurations of several recurrent papillary tumors of the urinary bladder Pathological reports always revealed a grade 2 papillary carcinoma of the urinary bladder

On January 25, 1956, the patient underwent total abdominoperineal prostatectomy and cystectomy, with a urinary diversion to an isolated loop of terminal ileum Postoperatively, a paralytic ileus developed despite pre- and postoperative Levine suction It was necessary to institute rectal lavages every three hours in order to facilitate the passage of gas On the eighth postoperative day an icteric tint to skin and sclera appeared The liver was enlarged and a diagnosis of hemolytic jaundice was made because the patient had had multiple transfusions (seven pints of blood) the day of surgery He recovered readily from this complication, but upon application of ileostomy bag blisters appeared around the ostium, necessitating the reinsertion of a size 30F Malecot catheter This type of catheter appears to be less irritating to the mucous membrane of the ileum The latter bleeds readily, and at times hemorrhages have been known to occur from an indwelling Foley catheter or overzealous dilatation of the ileostomy stoma After trying several types of urine-collecting apparatus, the patient found that the Singer cup was the easiest to apply and the least irritating to his skin

Preoperative retrograde pyelograms taken January 20, 1956 (fig 1, *A*), five

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Read at annual meeting of North Central Section of American Urological Association, Mackinac Island, Mich , August 29–31, 1957

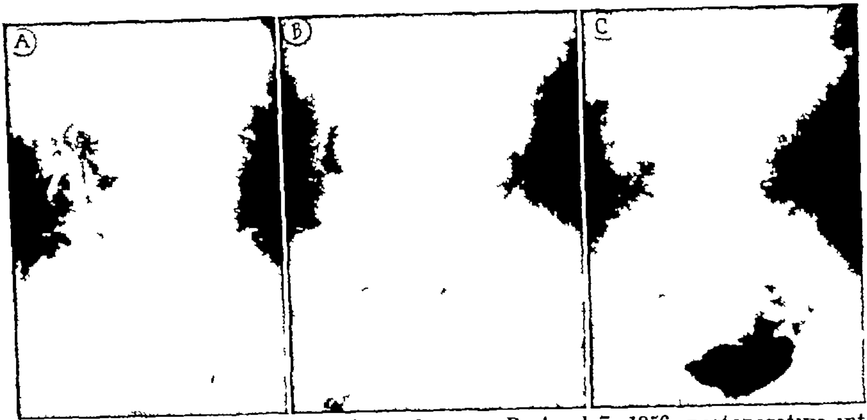

Fig 1 A, preoperative retrograde pyelogram B, April 7, 1956, postoperative intravenous pyelogram shows essentially normal left kidney with slight right pyelectasia and dilatation of upper third of right ureter C, impacted stone in right ureter opposite fourth lumbar transverse process

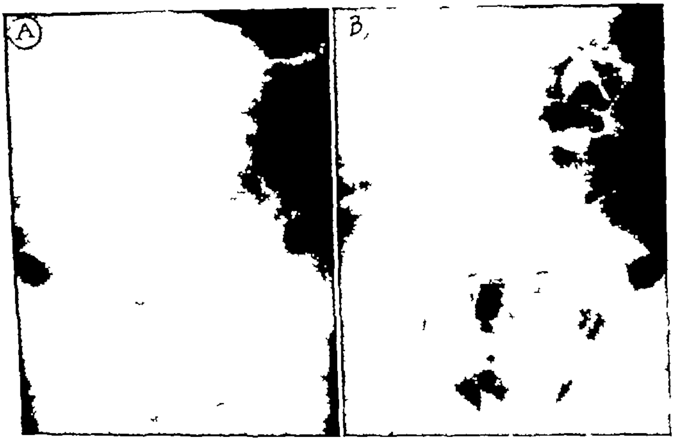

Fig 2 A, February 5, 1957, intravenous pyelogram shows recovery of right calyces and pelvis with dye in ileal bladder Right nephroptosis also present B, note recovery of right upper urinary tract after removal of right ureteral stone Left kidney essentially normal

days prior to surgery show an essentially normal upper urinary tract There was asymptomatic right nephroptosis

A postoperative intravenous pyelogram taken on April 7, 1956 (fig 1, *B*) showed an essentially normal left kidney with slight right pyelectasia and dilatation of the upper third of the right ureter This is probably the result of the right nephroptosis

On January 13, 1957, almost one year after the construction of the ileal bladder, the patient suffered right renal colic followed by the passage of several small calculi Hematuria occurred on January 15, and on January 20, the patient entered the hospital with chills, temperature of 103F, and severe right flank pain An intravenous pyelogram (fig 1, *C*) showed an impacted stone

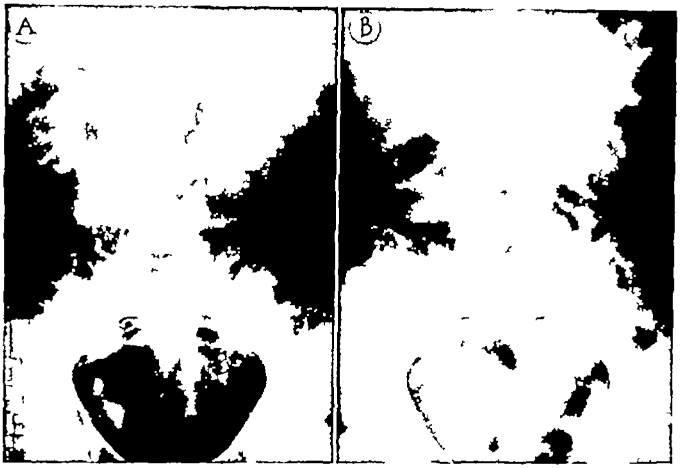

FIG 3 *A*, intravenous pyelogram shows nonfunctioning left kidney with stone impacted in upper third of left ureter Left nephrogram is present and right kidney is essentially normal *B*, *July 5, 1957, intravenous pyelogram shows recovery of left kidney and* dye in ileal bladder Right kidney shows slight nephroptosis

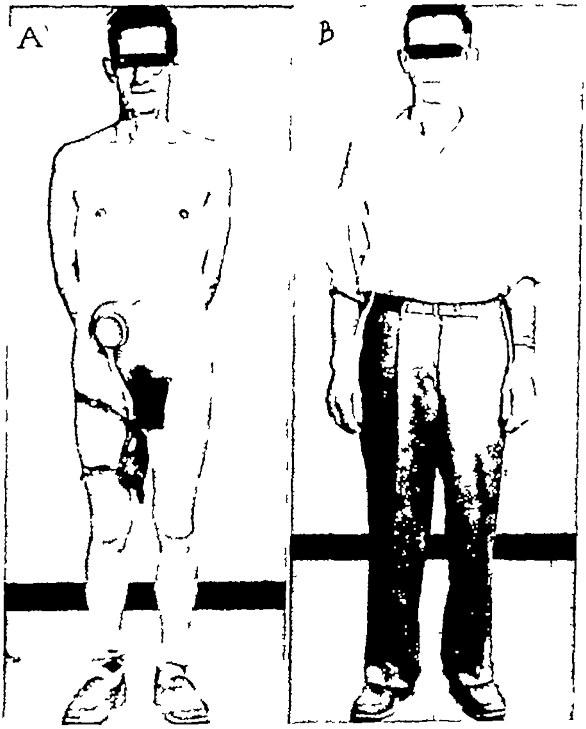

FIG 4 *A*, patient wearing Singer cup urine collecting apparatus and demonstrating healed *flank* incisions *B*, *patient in street clothes* Urine collecting apparatus not detectable

opposite the fourth lumbar transverse process with grade 2 caliectasia A ureterolithotomy was done and stone analysis revealed triple phosphates The patient made an uneventful recovery He was discharged on a proper diet and uromide An intravenous pyelogram taken February 5 (fig 2) showed a recovery of right calyces and pelvis and patency of the right ureter, since dye was present in the ileal bladder The left kidney was essentially normal

On May 27 the patient had an attack of left renal colic with symptoms of urosepsis and a blocked left kidney An intravenous pyelogram (fig 3 A) taken on admission to the hospital showed a nonfunctioning left kidney with a stone impacted in the upper third of the left ureter A left nephrogram was seen and the right kidney appeared essentially normal A ureterolithotomy was done from which recovery was uneventful Intravenous pyelograms on July 5 (fig 3 B) showed recovery of the left kidney, with dye in the ileal bladder The right kidney showed slight nephroptosis

Photographs of the patient taken on August 3 (fig 4 A) show him wearing his Singer cup urine-collecting apparatus and demonstrating the two healed flank incisions Another photograph (fig 4, B) shows the patient in his street clothes It is obvious that the urine-collecting apparatus is not detectable

The patient s urine has never been sterile on culture and it always contains several pus cells per high power field After almost one year with the ileal bladder the patient suddenly started forming triple phosphate calculi The nidus of the second calculus undoubtedly was already present when the patient was placed on a proper diet and medication Urine cultures and drug sensitivity tests were made and the patient placed on the specific drug In this instance it is gantrisin and not mandelamine or sodium acid phosphate and urotropin which renders the urine acid It seems that although mucosa-to-mucosa and serosa-to-serosa anastomosis of the ureter to the ileum tends to prevent stricture formation the mucus-secreting columnar epithelium of the ileum is not the transitional cell lining that the urinary tract needs to keep its urine sterile

SUMMARY

Early and late complications of the ileal conduit are listed and discussed The failure of the patient to keep his urine sterile and acid probably was the cause of his recurrent stone formation With a more conscientious adherence to proper diet and medication which keep his urine grossly clear and acid, we hope this complication will be avoided in the future

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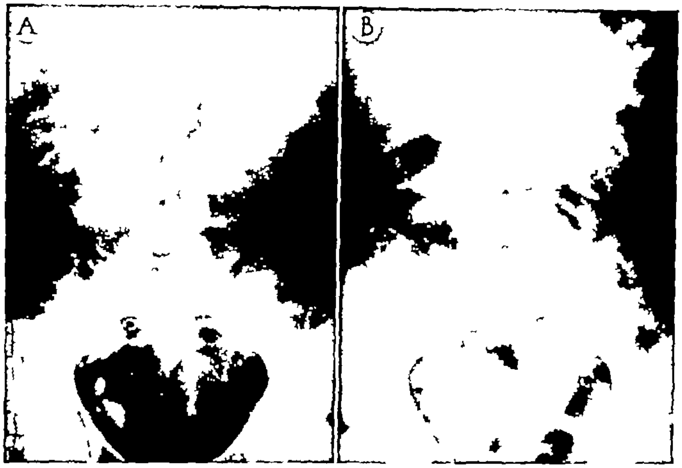

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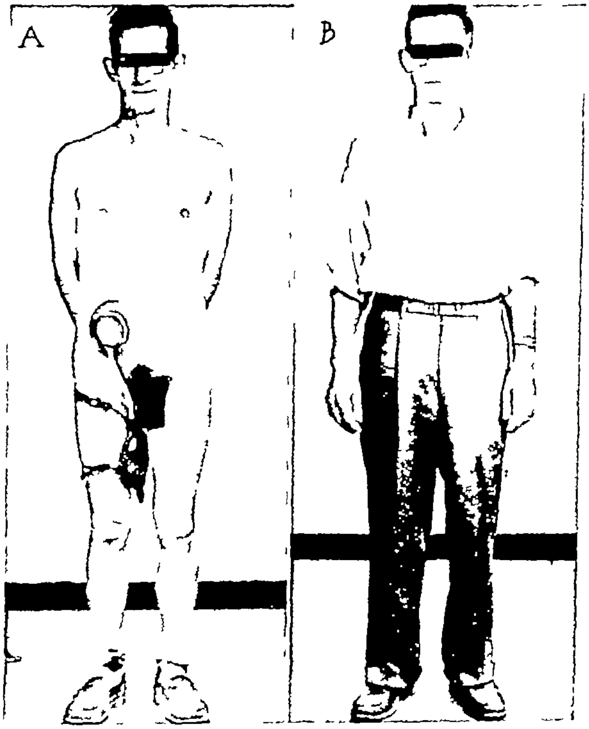

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VESICO-URETHROPLASTY FOR CONGENITAL VESICAL NECK OBSTRUCTION IN CHILDREN

BRADFORD W YOUNG AND JAMES D NIEBEL

From the Department of Surgery, Division of Urology, Stanford University School of Medicine, San Francisco, Calif

Congenital vesical neck obstruction in children has received some candid scrutiny in the past few years and several approaches to the problem have been investigated These include the conservative, consisting of urethral dilation, antispasmodic medication and antimicrobial therapy, and the operative methods, one of which is transurethral resection as a single or multiple stage procedure and—more recently—the somewhat more radical, open retropubic corrective surgery, which has been termed vesico-urethroplasty (fig 1)

As with many diseases, the variations in treatment may represent a certain confusion in diagnosis It would be attractive to assume that there is but one condition with varying degrees of severity, but this does not appear to be the case Formerly, bladder neck obstruction on a congenital basis had been very conveniently classified as either mechanical or neurogenic This is detailed very clearly by Emmett and Helmholz[1] in their excellent paper on the transurethral management of vesical neck obstruction This classification, however, excludes a number of children—mostly little girls—who appear to have some evidence of bladder neck obstruction, manifested by recurrent urinary tract infections with associated residual urine, who otherwise exhibit minimal objective evidence of obstructive disease

In male patients the incidence of severe mechanical obstruction with associated hypertrophy of the bladder, hydro-uretero-nephrosis and extensive renal damage has been reported to be at least three times that in females In our series we have been impressed with this severity of the disease in boys and the relatively minimal upper tract damage in girls At first we were content to attribute this to a mild form of the same process, but it may be that these cases are based on some ill-defined type of congenital neuromuscular insufficiency, as many of the men working closely with the problem suspect, rather than actual obstructive disease at the vesical neck

With this in mind we have made attempts to set some definite operative indications for vesical neck obstruction—taking into consideration the mechanical and neurogenic groups as well as a third category which might be called "dys kinesia" of the detrusor and sphincteric mechanisms This term was suggested in 1915 by Beer[2] and called to our attention by Dr Richards Lyon

The histological appearance of specimens removed from the vesical neck at the time of surgery should be of some value One might expect to find a greater fibrous component in specimens obtained from cases of severe mechanical ob-

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Accepted for publication October 24, 1957

[1] Emmett, J L and Helmholz, H F Transurethral resection of the vesical neck in infants and children J Urol , 60 463–478, 1948

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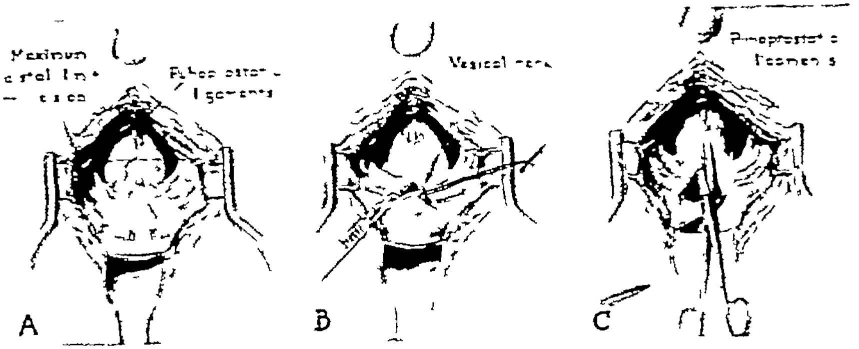

FIG 1 Semi-diagrammatic drawings of Y-V type of vesico-urethroplasty Incision is outlined in *A* It will be noted that distal limb of Y is kept above puboprostatic ligaments In female pubovesical ligament is analogous landmark. Incision can be most accurately made if hooked blade is used to make initial V as in *B* and prostatic urethra opened with scissors as in *C*

struction This did not prove to be the case in our series Sections stained by hematoxylin-eosin and van Geisen methods showed varying preponderances of smooth muscle fibrosis striated muscle and inflammatory reaction with little correlation of the pathological appearance of the tissue with the clinical findings in individual cases Pathologically, there was no 'typical' lesion associated with this syndrome or any of its clinical divisions

Classification was then based simply on clinical grounds and the usual subjective and objective evidences of bladder neck obstruction were used i e residual urine, trabeculation of the bladder, presence of upper tract dilatation, and renal damage The presenting symptoms are shown in the order of their rated importance in these conditions in figure 2 *A* The signs of lower urinary tract obstruction were reviewed as applied to children and these are shown with their relative weight in figure 2 *B* The diagram at the far right of both figures is merely a graphic representation of the physicians diagnostic assurance It will be noted that the more unreliable the sign the finer the point of insecurity, whereas in the presence of a number of diagnostic signs and symptoms one rests on a solid base

One of the difficulties encountered was establishing definite indications in borderline cases In many cases of recurrent urinary tract infection in which there appeared to be an obstructive element, there was minimal trabeculation of the bladder and no evidence of upper tract dilatation or vesical neck contracture With such variability of most of these findings more reliance was placed upon residual urine as a preoperative test This created a problem, for the measurement of residual urine with any degree of accuracy in children is, at best a difficult procedure In attempting to increase the value of this test we began using a floating radiopaque oil which fortunately was already available commercially as 10 per cent ascendant lipiodol*[2] and found it to be quite

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* E Fougera and Co

[2] Young B W Anderson W L and King G G Radiographic estimation of residual urine in children J Urol 75 263–272 1956

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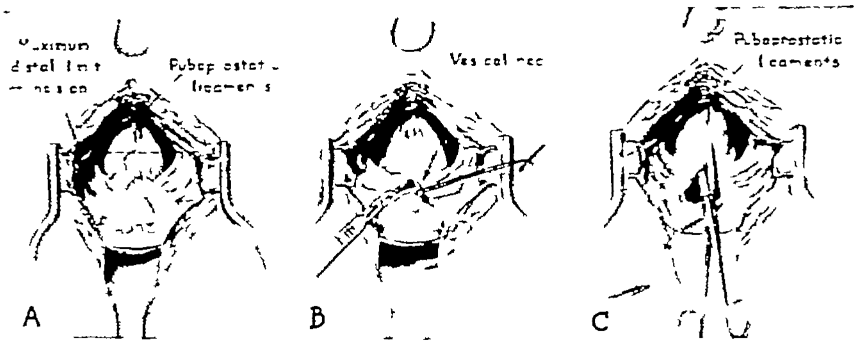

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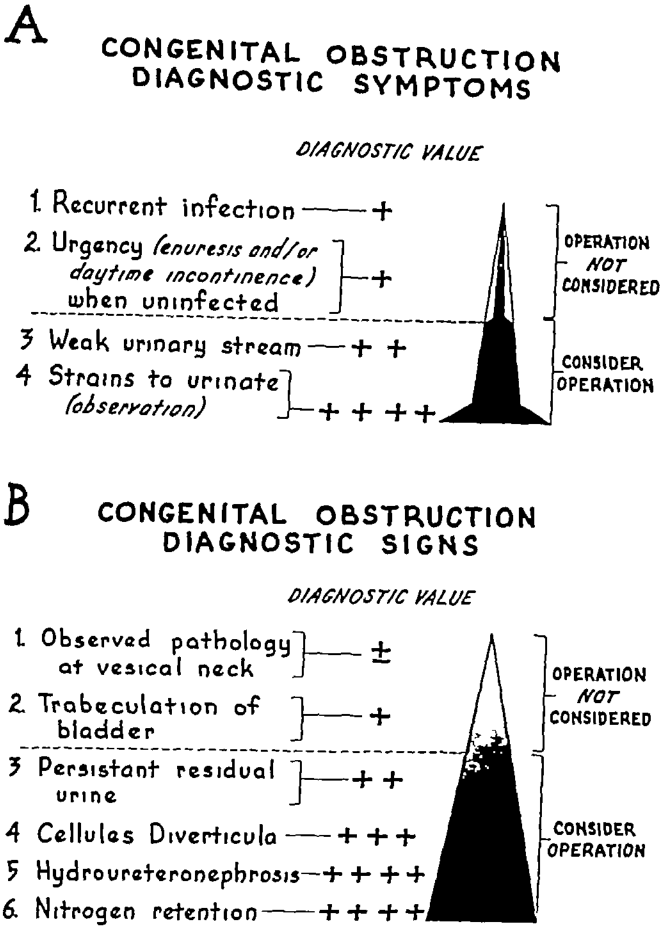
A
CONGENITAL OBSTRUCTION DIAGNOSTIC SYMPTOMS
DIAGNOSTIC VALUE
1. Recurrent infection — +
2. Urgency (enuresis and/or daytime incontinence) when uninfected — +
3 Weak urinary stream — + +
4 Strains to urinate (observation) — + + + +
OPERATION NOT CONSIDERED
CONSIDER OPERATION
B
CONGENITAL OBSTRUCTION DIAGNOSTIC SIGNS
DIAGNOSTIC VALUE
1. Observed pathology at vesical neck — ±
2. Trabeculation of bladder — +
3 Persistant residual urine — + +
4 Cellules Diverticula — + + +
5 Hydroureteronephrosis — + + + +
6. Nitrogen retention — + + + +
OPERATION NOT CONSIDERED
CONSIDER OPERATION

FIG 2 A, diagrammatic representation of weight placed upon most commonly noted symptoms of vesical neck obstruction *B*, diagrammatic representation of the diagnostic value of most common signs of vesical neck obstruction In cases with borderline signs and symptoms, management should probably be conservative

satisfactory The single most important sign in our experience has been the actual observation of the child voiding Our current feeling is that surgery should be considered when the diagnostic signs and symptoms fall below an arbitrary critical level drawn through each diagram

RESULTS

We have followed 20 cases of vesical neck obstruction subjected to vesicourethroplasty for periods ranging from two months to five years There were 11 males and nine females Secondary operation (i e , transurethral resection) was performed in one case Infection has persisted in 14 cases One patient died of renal failure and superimposed infection There was no operative mortality There was one case of total incontinence Stress incontinence, persisting for three and six months respectively, was encountered in two female children

Complete urinary control was regained by both of these patients Five operations were performed for frank neuromuscular dysfunction Fifteen operations were performed for what was presumed to be purely mechanical obstruction, however, four of these had minimal objective findings and might be classified in a "dyskinesia" group These results are summarized in table 1

TABLE 1 *Results in 20 cases of vesical neck obstruction subjected to vesicourethroplasty Most satisfactory results are associated with absence of residual urine*

Pre-Operative **Post-Op.**

CASE	MOS FOL	INFECTION	PERSISTENT RESIDUAL	SYMPTOMS	INFECTION	PERSISTENT RESIDUAL	SYMPTOMS
SW ♀ 4 yrs.	17	++++	+ Lipiodol	++++	++	0	++
S D ♀ 4 yrs	19	+++	+ Lipiodol	+++	+	0	0
K N ♂ 8 yrs	11	++	+ Lipiodol	++	+	+ Lipiodol	+
J.J.C. ♂ 3 wks.	38	0	125 cc	++++	0	+ Lipiodol	0
C.E ♀ 7 yrs.	37	++	45 cc	++	0	Trace Lip 48 hrs	0
M K ♂ 11 yrs	24	++	300 cc +	++++	+	20 cc	++
C.M ♀ 7 yrs.	42	+++	80 cc	+++	0	0	0
S L ♀ 9 yrs	42	++++	100-250 cc.	++	++	0-50 cc	++
L B ♀ 11 yrs.	24	++++	+ Lipiodol	++++	+	0	0
W R ♂ 21 yrs.	38	++++	10 cc	++++	+++	10 cc	+++
R N ♂ 8 yrs	24	++	1,200 cc	++++	+	0-25 cc	+
D R. ♂ 4 days	16	0	Partial reten. ? amount	Uremia	+	0	0
R S ♂ 13 mos.	10	+	300 cc +	++++ Renal fail	++	Supra pub. fistula	Renal failure
B D ♀ 9 yrs	12	+++	75 cc	++	++	?	++
L.F ♂ 7	36	++	+ Lipiodol	++	+	+ Lipiodol	0
R.B ♂ 2 days	60	0	40 cc	++++	+++	0	++++ Ren fail
G.S ♀ 5 yrs	6	++	+ Lipiodol	++	+	?	+
K.C. ♀ 7 yrs	21	++	+ Lipiodol	++	0	0	0
J.M. ♂ 35	2	+	50 cc	++	0	0	+
K.Mc. ♂ 11	56	+++	60 cc	+++	0	0	0

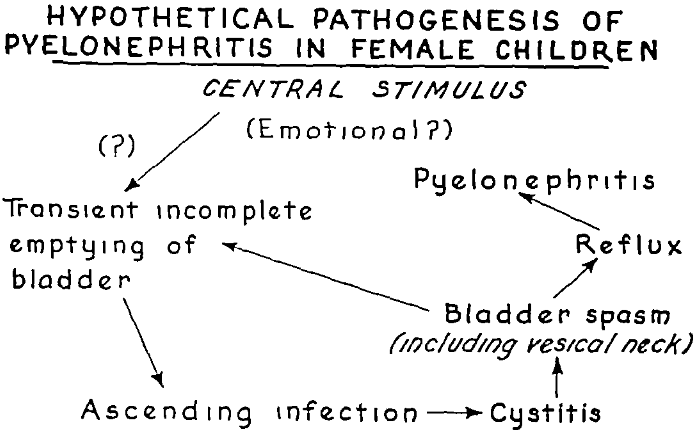
HYPOTHETICAL PATHOGENESIS OF PYELONEPHRITIS IN FEMALE CHILDREN
CENTRAL STIMULUS
(Emotional?)
(?)
Transient incomplete emptying of bladder
Pyelonephritis
Reflux
Bladder spasm (including vesical neck)
Ascending infection
Cystitis

FIG 3 Diagram of possible pathogenesis of pyelonephritis in female children

Some of these cases have been previously reported[4] and are included in this series as their evaluation is of importance

DISCUSSION

Congenital vesical neck obstruction in children, apparent or real, is quite a different situation from that which occurs in the adult In children there is little to see at the vesical neck, often highly questionable trabeculation of the bladder, and frequently no evidence of upper urinary tract damage It would be difficult to say that this even represents a disease if it were not for the episodes of recurrent infection and the presence of residual urine The suspicion is that the basic problem in many of these cases lies in the bladder musculature or its innervation—and this should include the possibility of a biochemical or enzyme system abnormality The condition has been reported in male siblings[5] which would seem to indicate that it is not an isolated developmental defect Bladder and vesical neck spasm may account for some cases We have seen female children with urinary tract infections who, during the acute phase of their infection, have had transient residual urine but when uninfected were able to empty their bladders completely It is possible that children from time to time—particularly under emotional stress—fail to evacuate their bladders totally, thus predisposing, especially in girls, to lower urinary tract infection

The pathogenesis of pyelonephritis in female children on purely hypothetical grounds, but based on some of these ancillary findings with regard to residual urine, is shown in figure 3 The hypothesis is that transient vesical neck spasm leads to residual urine which in females tends to become infected due to the short length of the urethra and the active motility of coliform organisms Reflux of the infected urine leads then rather directly to pyelonephritis This is consistent with the work of Bunge[6] and Montgomery Stewart,[7] both of whom have demonstrated reflux of urine to apparently normal kidneys with delayed cystograms In several of our cases there is very little doubt that reflux is the mechanism responsible for pyelonephritis Droplets of ascendant lipiodol have been noted to reflux freely to the kidney in cases showing changes of unilateral pyelonephritis and reflux

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One further word about the significance of residual urine, at the outset it was supposed that everyone capable of it could empty his bladder at a single voiding, provided that the bladder was not overdistended This, in children, was found to be too stringent a requirement, but it has been demonstrated by Mark Curtis,[8] in a series of fifteen controls, that children with normal urinary tracts evacuate their bladders completely of ascendant lipiodol in a twenty four hour period The "amount" of residual, though at times dramatic, is probably not greatly significant unless the amounts are quite large Curtis found that children who retained all of the lipiodol for a period of several days were more likely to need surgical relief than those who retained only a small percentage of the oil This latter group of patients could frequently be managed conservatively with good results In patients with immense amounts of residual urine and marked hydroureteronephrosis, the amount of residual urine in the bladder is quite difficult to determine as a portion of the urine may be retained in the renal pelvis and ureter The persistence of residual urine is the important thing, not only from a standpoint of susceptibility to infection, but also because it offers a reliable criterion for surgery With the many factors—some of them only partially understood—relating to persistent or transient residual urine, we are currently using the figure of seventy two hours as a significant period of retention of lipiodol

SUMMARY

Twenty cases of congenital vesical neck obstruction subjected to vesicourethroplasty have been studied These cases have been followed for varying periods from two months to five years All cases showed some improvement though complete cures were infrequent

No correlation could be established between the appearance of the pathological specimens removed at operation and the severity of the disease or its etiology

Our current criteria for operation are presented

Theoretical mechanisms of pathogenesis are discussed

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RETROPUBIC VESICOURETHRAL SUSPENSION

RUSSELL B CARSON

Retropubic or suprapubic suspensions of the bladder and urethra in the female have for the most part been developed by the general surgeon and the gynecologist The revival of interest in the retropubic space of the male by Terence Millin in 1948 and the valuable contribution by V Marshall, Marchetti, and Krantz in 1949 have failed so far to stimulate much interest in urologic circles toward vesical suspension procedures However, it is frequently the urologist who is consulted by the distressed female patient with a dripping or spurting bladder The prime reason for considering retropubic vesicourethral suspension procedures is in order to discuss a means of curing difficult cases of incontinence Therefore, urinary stress incontinence will consume most of our present interest

CLASSIFICATION OF STRESS INCONTINENCE

Urinary incontinence has been classified by John Ullery as 1) partial or 2) complete incontinence of one of the following types 1) congenital incontinence and 2) acquired a) postpartum, b) postmenopausal, c) postoperative

The retropubic suspension procedure is applicable only to those procedures which fall into the partial group and are usually of either the congenital, postmenopausal, or postoperative varieties Without question between 70 and 90 per cent of women with incontinence of the acquired or stress type can be cured either by conservative exercise or by one of the usual vaginal plastic procedures It is my belief that these eight of 10 cases belong to the gynecologist The two of 10 patients who belong in the classification of incontinence either of congenital or postoperative type are the ones who should concern the urologist It is those in this category in whom a careful urologic evaluation of the bladder function should be a preliminary to correction of the condition Nine out of 10 of these congenital or postoperative failures should obtain relief by properly selected suprapubic or retropubic repair Apparently from the statistics in the literature one in a hundred is going to fail regardless of the procedure used

ETIOLOGY

The etiology of stress incontinence, as described by Lich and Maurer, is "ptosis of the vesical neck," through the supporting structures of the pelvic diaphragm Whenever there has been either a failure of adequate formation of these supports or a breakthrough of the supports by childbirth, operative or other types of trauma, descensus of the urethra and base of the bladder is permitted Observed vaginally it is easy to see the "sliding" effect of the urethra under the symphysis and the bulging both downward and posteriorly of the base of the bladder into the vagina

Ullery summarizes the causes of stress incontinence as a) a failure of the "internal urethral sphincter" mechanism to maintain closure of the internal urethral orifice under conditions of exertion or stress, and b) failure of the bladder and urethral supports to prevent descensus of the neck of the bladder and urethra

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Read at annual meeting of North Central Section of American Urological Associations, Mackinac Island, Mich, August 29–31, 1957

DIAGNOSIS

A patient with stress incontinence, to be properly classified, should have the advantage of complete urologic evaluation prior to selection of a method of surgical correction Cystoscopic inspection of the urethra and bladder can demonstrate the activity of the voluntary sphincter and the degree of distortion of the urethrovesical angle Anteroposterior and lateral cystograms are valuable in assessing the degree of funneling of the vesical neck The upper urinary tract should be examined urographically Residual urine should be measured One should make a careful search to eliminate possible urinary tract anomalies or fistulas, urethral diverticula, etc Stress incontinence does have its urologic aspects

Retropubic, vesicourethral suspension is but one of many procedures which has been used to relieve urinary incontinence, but I believe that it has proven of sufficient value to occupy our interest for these few minutes

Sling operations such as Aldridge's (1942) combined approach, using fascia of the oblique muscles of the abdomen obtained by Pfannenstiel's incision to support the urethra by suturing the strips through a vaginal incision, or the procedure of Millin and Read, wherein fascial flaps are passed beneath the urethra from the suprapubic approach, have much to offer to correct stubborn cases I have not had experience with the sling procedures

Retropubic suspensions of the Marshall or Ball type have been used on nine occasions A few of these have been in association with vaginal repairs, where a descensus or a rectocele existed as well as a cystocele or cysto-urethrocele Of the 9 cases in which operation has been done, I have performed the suspension while a gynecologic surgeon has carried out any other vaginal or pelvic surgery that was indicated We have had eight successes and one failure After discussing our technique, a summary of our 9 cases will be presented

TECHNIQUE

Our technique of suspension has been primarily a Marshall, Marchetti, Krantz procedure, but with variations to meet circumstances We have used a transverse suprapubic incision through the rectus fascia and retraction of the recti laterally from the midline without cutting the muscles in all cases of simple retropubic suspension If the suspension was secondary to a pelvic laparotomy a vertical incision has been used by the gynecologist Our reasons for using the transverse incision are 1) it is our routine method of approaching the bladder or prostate, 2) because we have been expecting to do a sling operation some time for more adequate vesicourethral support, but thus far it has been unnecessary If a hysterectomy has been performed the opportunity is taken to plicate the anterior vaginal space using mattress sutures in the margins of the pubocervical fascia This adds support to the bladder and prevents formation of an enterocele

Complete mobilization of the lateral pelvic spaces to expose the anterior and lateral portions of the urethra, bladder and anterolateral surfaces of the vagina is accomplished The bladder is kept partially filled through a 5 cc Foley catheter, the bag of which helps to locate the vesical neck Usually two sutures of size 1 chromic catgut are placed on each anterolateral aspect of the urethra These are tied to assist hemostasis Two or three sutures are then placed on either side of the bladder at the vesicovaginal margin We have not tried to make the imbricating stitch, as described by Marshall, in this area because it does not seem to be necessary After all sutures have been placed in the urethra and bladder, their approximate apposition to the pubis is ascertained A good bite is taken with each suture individually into the periosteum of the pubis After all have been thusly placed, they are tied beginning with the deepest, most median urethral suture and progressing outward to the most superior lateral suture The space of Retzius should be closed when all sutures have been tied Bleeding is sometimes troublesome while the sutures are being placed in the urethra and at the vesical neck, but will have stopped by the time one is ready to tie the sutures The lateral spaces are drained with a Penrose drain in each space The fluid in the bladder is withdrawn at the conclusion of operation to ascertain whether intravesical trauma has been produced by the sutures The vagina is usually packed with gauze for 48 hours to decrease the possibility of tension on the sutures in the bladder

CASE REPORTS

Case 1 Mrs L M , No BG 66505, aged 63 years, was first seen September 1953 with the chief complaint of constant dripping of urine day and night and occasional "spurts" of urine during the day She was using from six to eight perineal pads daily The patient had never been pregnant

Examination revealed no evidence of urethrocele or cystocele Cystoscopic examination revealed a shortened urethra Little or no sphincteric action could be seen through a panendoscope or on command to void or hold urine Careful examinations excluded the possibility of fistula, anomalous ureteral opening or neurologic lesion

January 24, 1955, a retropubic suspension of the urethra and bladder was done following the method of Marshall and associates

The result was good Complete night and day continence was achieved until the patient took an automobile trip of two thousand miles in June 1955 (six months after surgery), following which she experienced a return of both the constant drip and the spurts of urine Cystoscopic examination did not reveal any apparent change in the urethrovesical relationship

She was operated upon again December 19, 1955, in a large midwestern clinic An urethral advancement operation did not afford relief from the incontinence This case was certainly our failure, that is, until a fall in May 1957 resulted in a compression fracture of the second lumbar vertebra Following the accident the patient obtained sudden and complete continence as far as the drip of urine was concerned An occasional spurt of urine occurs once or twice a day when the bladder is fairly full of urine

Case 2 Mrs P McG , No BG 70293, aged 46 years, was first seen May 1955, with the complaint of constant leakage of urine of three years' duration She wore perineal pads constantly The patient had one child 26 years of age She had undergone pelvic surgery 14 years before she consulted us

Examination revealed a grade 3 urethrocele, a cystocele and a moderate rectocele

On June 16, 1955, a combined anterior and posterior repair was made by a gynecologic colleague while an assistant and I suspended the bladder suprapubically after the bladder and urethra had been separated from the vagina and cervix The bladder and urethra were suspended to the posterior surface of the pubis, the space of Retzius being closed with great care and no tension on the sutures

This is the only combined procedure we have done with both teams working at the same time but it yielded one of our most satisfactory results This patient has had excellent control for the past two years Would the single procedure from below have given the same good result? Perhaps, but anyway the combination has produced a perfect result

Case 3 Mrs D G, No BG 70168, aged 34 years, was first seen in January 1954, complaining of urinary frequency, dysuria, loss of urine on stress, chronic pelvic pain, and severe dysmenorrhea

She had had one pregnancy five years previously No pelvic operations had been done

Examination disclosed a grade 2 cystocele but a markedly mobile urethra Stress incontinence was demonstrated with a partially filled bladder while the patient was on the examining table in the lithotomy position A gynecologic consultant advised pelvic surgery for probable endometriosis and uterine myomas

Operation June 13, 1955, following a hysterectomy by a gynecologic surgeon, we performed a retropubic urethrovesical suspension This was done to save the patient an operation for vaginal repair

The result was almost too good, because for a short period after surgery she had some difficulty starting the urinary stream No incontinence has occurred during the past 2 years

Case 4 Mrs B W K, No BG 76948, aged 67 years, was first seen in March 1948, at which time she gave a history of ten years of urinary stress incontinence and repeated urinary tract infections

In March 1949, a vaginal repair was followed by relief of the incontinence for approximately one year In 1952, I re-examined her because incontinence had returned The cystocele had recurred but there was no urethrocele Pessary support of the cystocele resulted in control of the incontinence

Operation On February 29, 1956, a retropubic vesical suspension of the Marshall type was done

The patient has had complete continence for the past 14 months Vaginally and cystoscopically there is excellent support of the bladder

Case 5 Mrs M C, No HC 1222, aged 72 years, was first seen January 1, 1956, complaining of inability to hold urine for 10 years She found it necessary to wear perineal pads during the day A cystocele repair and hysterectomy had been done 22 years previously

Examination revealed a pronounced degree of mobility of the urethra a severe enterocele with cystocele but no rectocele or perineal relaxation

Operation On March 12, 1956, a retropubic vesicourethral suspension was performed We did not plicate the vesicovaginal area as we should have done

Result The decision to perform retropubic suspension was made because previous vaginal surgery had been done and there was evidence of poor musculofascial supports The retropubic suspension has resulted in complete urinary control for fifteen months so far Cystoscopic examination disclosed a good urethrovesical relationship and a full bladder showed no evidence of a cystocele An enterocele was present at the conclusion of the procedure and I failed to obliterate it by vaginal plication behind the bladder

Case 6 Mrs N I, No HC 1744, aged 46 years, had complete urinary incontinence that required the wearing of many pads daily She had undergone vaginal plastic repairs in 1946, 1950, and 1953, none of which successfully controlled the leakage

Examination revealed a moderate urethrocele with mobility on effort, a grade 2 cystocele and leakage of urine with the patient in the lithotomy position

A Marshall operation was done on April 4, 1956

Excellent anatomic and functional control was present as of June 11, 1957

Case 7 Mrs M J H, No BG 80335, aged 49 years, gave a history of stress incontinence of 10 to 15 years' duration, but a complete loss of control required perineal pads all day two months prior to the first examination A vaginal repair in 1951 had been unsuccessful

Examination revealed marked sliding of the urethra beneath the symphysis on effort Sufficient vesicourethral angulation was present to require a right angle lens for inspection of the trigone, with the bladder partially filled

Operation (July 11, 1956) was done in association with a gynecologic surgeon In addition to suspending the bladder to the posterior surface of the pubis, the vesicovaginal space was opened and a plication made for further support

Result The patient has been continent during the past year Anatomically she has excellent vaginal supports

Case 8 Mrs L V, No BG 85718, aged 55 years, underwent vaginal repair for urinary incontinence in July 1956 I saw her six months later, at which time she had a recurrence of both cystocele and incontinence In addition, she had a chronically infected cervical stump and a palpable cystic left ovary A gynecologic consultant advised removal of the left ovary and cervix A combined procedure was performed at which I suspended the bladder and plicated the vagina after the left ovary and cervix had been removed

Case 9 Mrs A H, No BG 86905, aged 35 years, presented a history of urinary incontinence on stress of 2 years' duration She had delivered one child 14 years previous to examination

Examination revealed a moderate urethrocele and cystocele, no rectocele, a large, hard, fibrotic uterine fundus and severe laceration of the cervix A gynecologic consultant advised complete hysterectomy together with a retropubic vesicourethral suspension This was done March 14, 1957 The anatomic result appears excellent and no incontinence has occurred during the short period of observation, i e, three months

A completely co-operative gynecologic department is necessary to achieve results such as we have described in these nine patients I have omitted a description of all routine details, i e , a cystoscopy, an upper tract study by x-rays, cystograms, and other usual procedures for proper case evaluation

INDICATIONS FOR RETROPUBIC VESICOURETHRAL SUSPENSION

The foregoing brief case histories have illustrated some of the indications for the operation Urinary incontinence not accompanied by evident urethrocele or cystocele

Incontinence persisting after one or more unsuccessful vaginal repair procedures

Incontinence associated with intrapelvic disease necessitating laparotomy

Incontinence wherein there is evidence of inherently poor urethral and vesical supports

Conceivably the procedure can be used also a) as a prophylactic against post-menopausal incontinence when pelvic surgery is necessary for some other reason, and b) if vulvar, vaginal, or cervical infection, hip joint ankylosis and the like make a vaginal approach undesirable

COMMENTS

Retropubic vesicourethral suspension has proven to be a valuable procedure for handling certain selected difficult problems of urinary incontinence

Stress incontinence is not the same problem in the male as in the female patient because there is seldom loss of the suburethral and subvesical supports In the male we may be able to prevent those occasional occurrences of post-prostatectomy incontinence by more attention to vesical neck suspension in the retropubic procedure After a suprapubic procedure the vesical neck should be elevated as much as possible and a minimal accordian effect produced by heavy tension on a hemostatic bag

I wonder if any of my colleagues have attempted to cure an enuretic youth by means of a suprapubic vesicourethral suspension I have been wondering for a long time if such a procedure would meet with success but have not had an occasion to test the idea

Retropubic vesicourethral suspension is a valuable procedure that is used almost exclusively by the gynecologic surgeon, unfortunately by not many of them, otherwise fewer vaginal repair procedures would have to be repeated with continued failures

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A completely co-operative gynecologic department is necessary to achieve versely through one testis and sagittally through the other In 142 autopsies, only one testis each was made available for this study In most instances, the tunica albuginea, rete testis, epididymis, and testicular parenchyma were available for examination Fixation of all specimens was in 10 per cent neutral formalin All sections which showed the EPLC with the hematoxylin-eosin method were treated with Gomori's trichrome, argentaffin, chromaffin, and oil-red-o stains Special note was made of the location of the Leydig-like cells and their association with other structures

RESULTS

There was no correlation between the size or gross appearance of the testes and the presence of the EPLC

Microscopic examination of the hematoxylin-eosin sections revealed the presence of Leydig-like cells in the tunica albuginea in 200 of the autopsies (67 5 per cent), in the rete testis in 35 (11 8 per cent), in the adventitial tissue between the tunica albuginea and the epididymis in 7, in the epididymis in one autopsy (fig 1), and associated with the vas deferens in one

The morphology of the EPLC was identical with the interstitial Leydig cells of the parenchyma The cytoplasmic activity of the EPLC in any single section mirrored that of the parenchymal Leydig cells in relation to the presence of granules, vacuoles, and pigment The nuclear appearance of the parenchymal Leydig cells and the EPLC was indistinguishable

In the tunica albuginea, these cells were observed in small and large groups, occasionally as large nodules (fig 2) and not infrequently as scattered groups of 3–10 cells The cells were arranged in linear fashion along the course of nerves or vascular channels The EPLC are arranged in large and small groups in a para-nerve position, and occasionally the cells may be located within the nerve (fig 3) Their association with vascular channels is that of an intimate paravascular position, sometimes completely surrounding the blood vessel (fig 4) The association of these cells with blood vessels occurred in 27 per cent, with nerves in 10 1 per cent, with blood vessels and nerves in 6 4 per cent, there was no association with a specific structure in 56 5 per cent

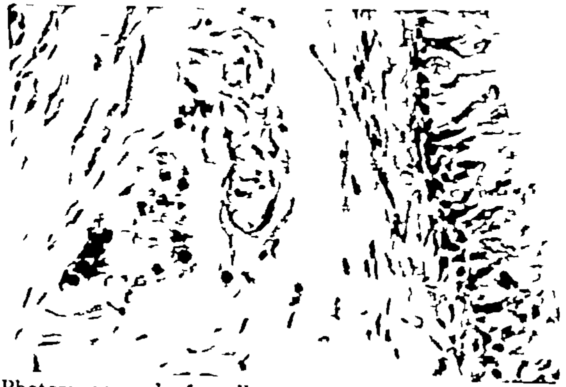

FIG 1 Photomicrograph of small group of Leydig like cells in epididymis

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A HISTOLOGICAL STUDY OF EXTRAPARENCHYMAL LEYDIG-LIKE CELLS

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This study deals with the histological examination of a group of human testes to determine the presence of extraparenchymal Leydig-like cells (EPLC),* to establish their incidence, to correlate their presence with pathological processes, age, endocrine organs, and testicular parenchymal cytology, and to suggest a possible clinical application of this study

The common occurrence of the EPLC has in general been disregarded Many who have reported their presence have seemingly been unaware of the high incidence of these cells in the tunica albuginea[1-3] Oberndorfer states that they are seen in the tunica albuginea, rete testis, and epididymis "where they do not occur normally"[4] However, Nelson found Leydig-like cells frequently in the tunica albuginea in his study of 481 testes[5]

The most extensive investigation of the EPLC has been carried out by Berger[6-8] He has shown these cells to be chromaffin and argentaffin negative, lipoid positive, morphologically identical to the parenchymal Leydig cells, and to bear a curiously intimate relationship to nerves within the tunica albuginea and the rete testis De Winiwarter believed the EPLC to be pheochrome cells[2, 7] However, Berger found both true chromaffin cells and the EPLC in the same sections and demonstrated morphologically and by differential stains the non similarity of the cell types[9]

MATERIALS AND METHODS

The testes and epididymides were secured from 296 consecutive male autopsies Examination was made by pairs in 154 autopsies with sections made trans-

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Read at annual meeting of North Central Section of American Urological Association, Mackinac Island, Mich , August 29–31, 1957

* For the purpose of brevity, the extraparenchymal Leydig like cells will be designated by EPLC

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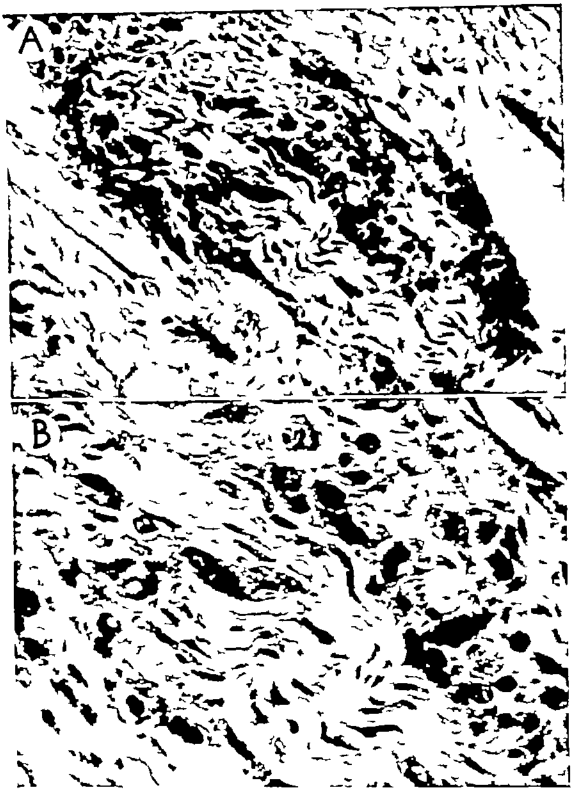

Fig 3 *A*, photomicrograph of non myelinated nerve at junction of rete testis and tunica albuginea with Leydig like cells within nerve and in a para nerve position *B*, higher magnification of nerve shown in A illustrates nuclear and cytoplasmic detail of Leydig like cells within nerve

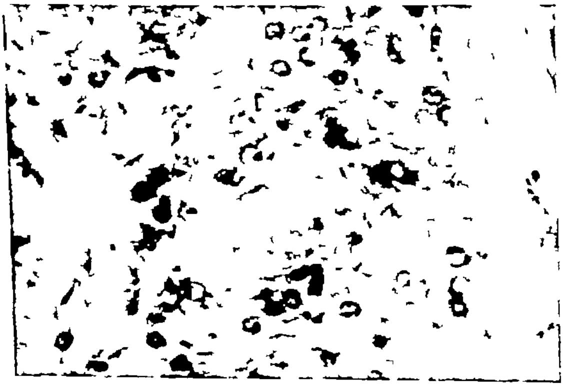

Fig 4 Photomicrograph of group of Leydig like cells surrounding blood vessel within tunica albuginea

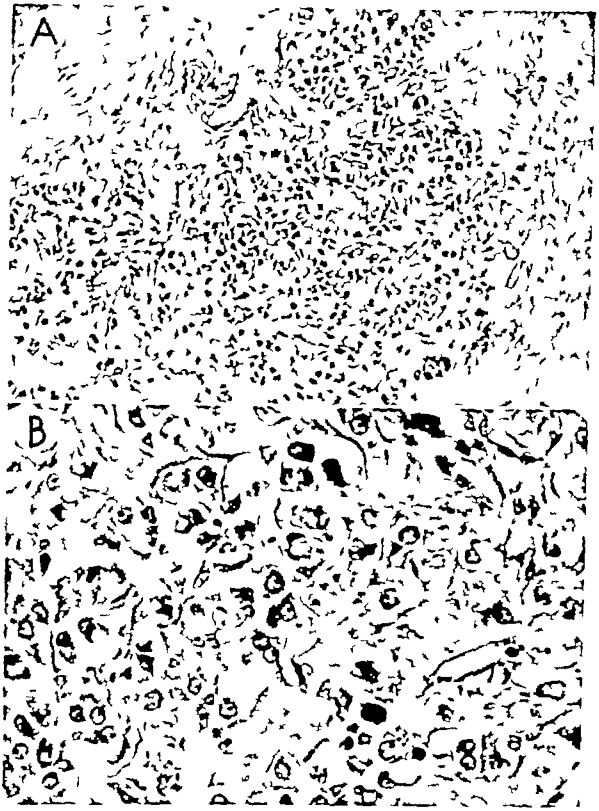

FIG 2 *A*, photomicrograph of nodule of Leydig like cells within tunica albuginea *B*, higher magnification of nodule shown in A illustrates detail of Leydig like cells with granules and vacuoles within cytoplasm

The EPLC in the tunica albuginea were found in varied locations from the tunica vasculosa to just beneath the outer surface layer, though the majority were located between the inner and middle thirds and the center of the tunica albuginea In all instances of positive findings, these cells were well within the tunica and not just adherent to its inner edge On occasion, large groups of *these Leydig-like cells invaded deep into the tunica albuginea from the parenchyma*, maintaining a direct contact with the parenchymal Leydig cells and indistinguishable from them

In the rete testis, the EPLC were generally in groups of 20 cells and more, and it was unusual to find association with either nerves or blood vessels (fig 5, *B*) These cells are also identical in appearance to the Leydig cells of the testicular parenchyma

Gomori's trichrome stain enhanced the *identification* of the EPLC, the red nucleus and lighter cytoplasm were vividly apparent against the green fibrous tunica albuginea The nerve fibers and the Reinke crystalloids are also much more apparent with this stain than with the hematoxylin-eosin

Reinke crystalloids were seen infrequently within the cytoplasm of the Ley-

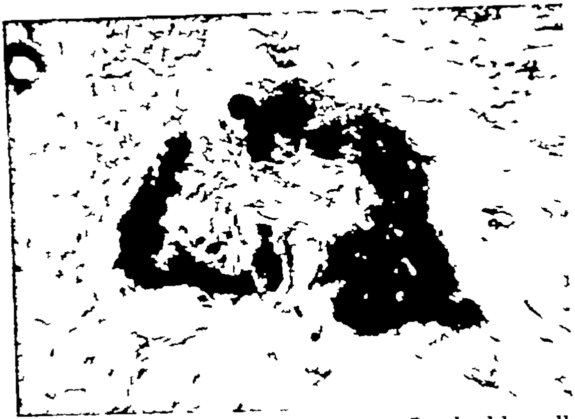

FIG 6 Photomicrograph showing lipoid containing Leydig like cells associated with both nerve and blood vessel within tunica albuginea

TABLE 1 *Incidence of Leydig like cells in extraparenchymal locations*

Age	No Cases	Tunica Albuginea	Rete Testis	Other
0–9	8	0	0	0
10–19	7	4	2	0
20–29	11	7	1	0
30–39	16	11	0	2
40–49	29	18	3	1
50–59	75	39	9	2
60–69	88	66	7	3
70–79	42	36	8	0
80–89	20	19	5	1
Total	296	200	35	9

dence of Leydig-like cells from 57 per cent in the 10–19 to 95 per cent in the 80–89 age group (table 1) Statistically this was apparently a true incidence trend associated with an increase in age The figures of both the 50–59 and the 60–69 age groups statistically appeared to be sampling errors, one incidence too low (50–59 group) and one too high (60–69 group) In the groups below age 59 the incidence was below the expected results while in groups above age 59 the incidence was above the expected results, again indicating the trend of increase in incidence with age

DISCUSSION

This study agrees with the investigations of Berger and others,[10] [11] with the exception of the association of the EPLC with nerves Because of the relationship of these cells with the non-myelinated nerves of the rete and tunica of the testis, Berger called them “sympathicotrophic cells” and postulated a neuro dig-like cells of the tunica albuginea (fig 5, *A*) On occasion, they were numerous in a given section, comparing well with the frequency of the crystalloids in the parenchymal Leydig cells of the same section In only one instance were the crystalloids seen in the Leydig-like cells which were located within a nerve

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[10] Wieser C Über die Hiluszellen der Keimdrüsen insbesondere im Vergleich mit den Leydigschen Zwischenzellen I Endokrinologie 8 321–335 1931

[11] Okkels, H and Sand K Morphological relationship between testicular nerves and Leydig cells in man J Endocrinol 2 38–46 1940

The argentaffin and chromaffin stains gave entirely negative results indicating that the EPLC are not pheochrome cells

The oil-red-o stain consistently showed lipoid in the cytoplasm of the Leydig like cells in all extraparenchymal locations (fig 6) The amount of lipoid present matched that within the Leydig cells of the parenchyma in any given section

Difficulty was encountered in definitely identifying Leydig-like cells within the tunica albuginea and the rete testis of the stillborn and infant testes

Correlative studies of clinical disease and pathological findings with EPLC were negative In those individuals in whom EPLC were found, examination revealed no correlation with alterations from the normal in the adrenals, pituitary, thyroid, or parenchymal testicular tissue However, age correlations revealed a definite trend The incidence of extraparenchymal Leydig-like cells in the tunica albuginea was greater with the increase in age With the exception of a 52 per cent incidence in the 50–59 age group, there was a gradual increase in inci-

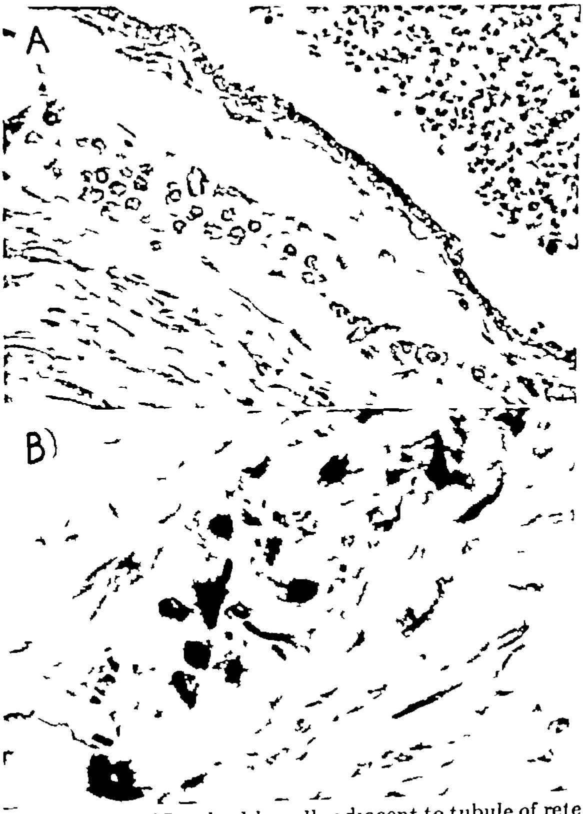

FIG 5 *A* photomicrograph of Leydig like cells adjacent to tubule of rete testis *B* photomicrograph of Reinke crystalloids within cytoplasm of Leydig like cells within tunica albuginea

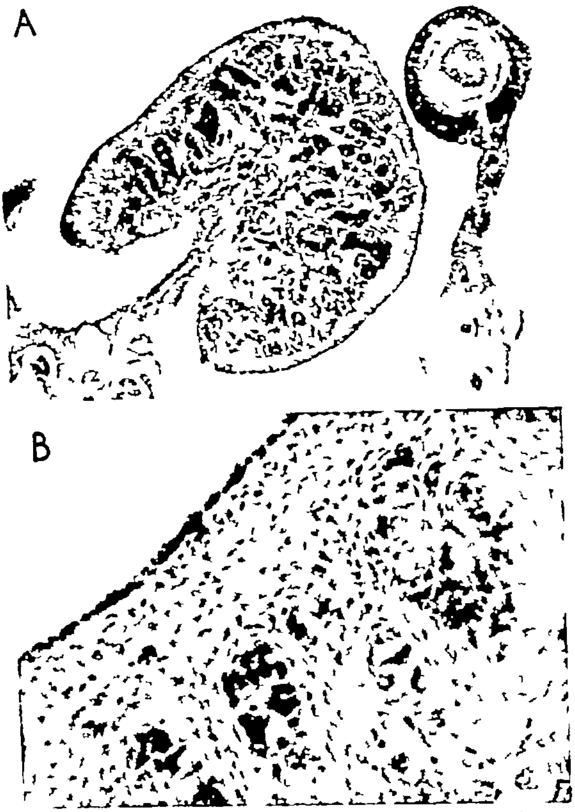

Fig 7 A photomicrograph of testis of 32 mm human embryo shows testis cords and intermediate cords and early formation of tunica albuginea at periphery (Human embryo, 32 mm series 21 No 111, courtesy Department of Anatomy University of Illinois College of Medicine) *B*, higher magnification of testis shown in A Note loose arrangement of cells in peripheral area destined to become tunica albuginea and intimate relationship to cells of intermediate cords

cords (fig 7)[15] [16] It is quite possible that there is intermingling and migration of some of the genitaloid cells of the intermediate cords with penetration into the loosely arranged cells of the tunica albuginea Sufficient time seems to be available for this to occur, as the development of the connective tissue of the tunica is from the periphery inward with the loose arrangement of cells in the tunica apparent to at least the 104 mm (CR) embryo The genitaloid cells might also follow the easy path through the tunica along the vascular and nerve pathways which are being formed in the 13 to 20 mm embryo

Tuovinen and Pohjola,[17] in the belief that the EPLC were rather commonly tropic function[8] However, he also referred to them as "regular" Leydig cells Only occasionally was he able to show nerve fibrils and end organs in intimate association with the Leydig cells of the parenchyma, though these findings may have been inconsistent due to the inconstancy of the nerve staining methods[6] However, he believed the consistent relationship of the EPLC cells with the nerves of the rete and the tunica and their morphological identity with the parenchymal Leydig cells to bolster the claim of a neurotropic function for Leydig cells

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[15] Keibel, F and Mall, F P Manual of Human Embryology Philadelphia and London J B Lippincott vol 2, 1912

[16] Patton B M Human Embryology, 2nd ed New York and Toronto The Blakiston Co 1953

[17] Tuovinen, P I and Pohjola R The importance of the epididymis in castration Acta Endrinocologica 3-4 1-16 1949-50

Others have found Leydig cells to be primarily associated with vascular channels or to have no special association[2, 12, 13] Berger agrees that in many instances the Leydig cells in the tunica albuginea and the rete testis appear to be associated with blood vessels but believes this orientation is because of vascular and nerve pathway association with the nerves not being demonstrable[6] Nelson reported Leydig-like cells in the hilus and tunica albuginea in 194 of 481 testes examined, with groups of these cells associated with nerves in 109 testes[5] We observed the Leydig-like cells associated with nerves alone or with nerves and blood vessels together in only 16 5 per cent of the autopsies

The presence of Reinke crystalloids in the cytoplasm of the Leydig-like cells in the tunica albuginea and the rete testis further emphasizes the similarity of these cells with the Leydig cells of the testicular parenchyma

It appears to be well established that these cells are not chromaffin cells[2, 5, 9] This may be augmented by the correlation of age with the incidence of the extraparenchymal Leydig-like cells and the presence of lipoid in these cells in in the adult In this study, the incidence of the EPLC increases from 10 to 89 years with the highest incidence in the 80 to 89 age group Lipoid is commonly found in the cytoplasm of these cells in the adult Chin observed adrenal rest tissues in the testes of only 1 6 per cent of males in the 16 to 83 age group and an absence of lipoid in the adrenal rest cells of the adult testis[14]

There is a rather simple embryological explanation of the presence of the Leydig-like cells in an extraparenchymal location with or without vascular or nerve association The tunica albuginea and the rete testis are derivatives of the epithelial nucleus that forms the testis cords (seminiferous tubules) and the intermediate cords (interstitial tissue) These cords are seemingly formed all at one time in the 13 mm embryo or later The intermediate cords are composed of indifferent and genitaloid cells, with the indifferent cells later disappearing for the most part and the genitaloid cells becoming interstitial (Leydig) cells At the time of the intermediate cord formation, the tunica albuginea appears and represents the peripheral portion of the epithelial nucleus The tunica at first is composed of scattered round cells which are loosely arranged with more or less direct contact and intimate association with the underlying intermediate

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[12] Brack, E Zur pathologischen Anatomie der Leydigzelle Virchow's Arch f path Anat , 240 127–143, 1923

[13] Priesel, A Über das Verhalten von Hoden und Nebenhoden bei angeborenem Fehlen des Ductus deferens, zugleich ein Beitrag zur Frage des Vorkommens von Zwischenzellen im menschlichen nebenhoden Virchow's Arch f path Anat 249 246–304 1924

[14] Chin S Pathologisch anatomische und histologische Untersuchungen über die Gewebsmissbildungen im Hoden Gann, 31 727–732, 1937

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ANDROBLASTOMA OF THE TESTICLE REPORT OF A CASE IN AN INFANT 3½ MONTHS OLD

AZIZ FAM AND KAMAL G ISHAK*

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Patient R M S , an Egyptian male infant three and one half months old, was reported by his mother to show a progressive increase in the size of his left testicle of one month's duration Pain had not been present, as evidenced by the absence of any unusual crying A general practitioner had already seen the child and had prescribed a fortnight's course of penicillin and streptomycin without any apparent diminution in the size of the swelling

On examination it was noted that the general condition of the child was excellent The pulse, temperature, skin and mucous membranes were within normal limits The breasts were not enlarged There was no lymphadenopathy in the axillae, supraclavicular regions or groins The lungs and heart were normal to palpation, percussion and auscultation Abdominal palpation revealed no ascites or intra-abdominal swelling

Local examination of the scrotum showed enlargement of the left side, but no impulse was present when the child cried The swelling was wholly intrascrotal, was oval in shape, and was about 5 cm in its greatest dimension The surface was smooth with a few indistinct bosses, and the consistency firm A small amount of fluid was detected by pinching The epididymis could not be palpated separately from the swelling Thickening of the cord was noted, but there was no matting of the cord structures and no masses could be felt The intrascrotal contents on the right side were within normal limits The size of the penis corresponded to the age of the patient Laboratory analyses, including a Wassermann reaction, revealed negative findings Hormonal assays were not attempted in view of the fact that signs of endocrinal imbalance were not present

A tumor of the testicle was suspected and consequently a left orchiectomy was performed, with excision of the cord as far as the internal abdominal ring The wound healed by first intention in seven days and the child was discharged from the hospital He has been regularly followed up for a period of two years and is alive and in good health up to the present time

The gross specimen (fig 1) consisted of the diseased testicle, the epididymis and the spermatic cord The enlarged testicle measured 3½ by 2 by 2 cm and was invested with an intact tunica vaginalis A small amount of clear, straw-colored fluid flowed out when the parietal layer was incised The visceral surface of the tunica vaginalis was smooth and glistening Section of the testicle revealed that its consistency was firm The cut surface was opaque, homogeneous, and greyish white in color The normal structure of the testicle was not present Distinct lobulation was noted, the lobules being separated by depressed fibrous trabeculae, and measuring between 0 5 and 0 7 cm in diameter No areas of

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located in the epididymis,[1, 13, 18, 20] felt that it should not be left in situ in therapeutic orchiectomy for adenocarcinoma of the prostate Their studies in the rat were without significant results This might have been anticipated in view of van Campenhout's work showing the limitation of EPLC to primates[21, 22] In addition, Berger does not believe the epididymis to be the usual site of EPLC in the human[6] In accord with Berger, we found EPLC in the epididymis on only one occasion

Amelar recently reported a case of anorchism without eunuchism[23] At surgical exploration, a group of Leydig cells were found along the vas deferens This absence of eunuchoid characteristics is apparently indicative of the functional capacity of these extraparenchymal Leydig cells

The presence of considerable numbers of Leydig-like cells within the tunica albuginea and the rete testis of a single section of the testis would lead to the assumption that in the entire tunica and rete of the testis there could be a significant amount of these cells Also, if single sections of the testis reveal these cells in the tunica albuginea in 67 5 per cent of the autopsies examined, it might indicate that a greater number of sections would have shown the Leydig-like cells within the tunica of all the testes

If these extraparenchymal cells are true Leydig cells and, as such, are productive of androgen, there is the possibility that in performing a subcapsular orchiectomy sufficient functioning androgenic tissues may be left to continue stimulation of an adenocarcinoma of the prostate Until knowledge is available of the fate of these cells in the tunica albuginea following subcapsular orchiectomy or until it can be proved that they are not functioning Leydig cells, total orchiectomy should be performed in the treatment of adenocarcinoma of the prostate

SUMMARY

In a study of 296 patients at autopsy, Leydig-like cells morphologically identical with the parenchymal Leydig cells were found in the tunica albuginea in 200 individuals, the rete testis in 35, the extratesticular adventitia in 8, and the epididymis in one

These extraparenchymal cells do not in this study show especial association with nerves in the tunica albuginea and the rete testis

The incidence of these extraparenchymal Leydig-like cells increases with the individual's age, being greatest in the 60–89 age group

Total orchiectomy should be performed in the treatment of adenocarcinoma of the prostate until knowledge is available of the fate of these extraparenchymal Leydig-like cells following subcapsular orchiectomy

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[18] Berblinger, W Über die Zwischenzellen des Hodens Verhandl d deutsch path Gesellsch , 18 186–197, 1921

[19] Snellman, B A case of tumor like hyperplasia of the interstitial cells in the testis Am J Cancer, 35 258–263, 1939

[20] Maximow A A and Bloom W A Textbook of Histology, 6th ed Philadelphia and London W B Saunders Co , 1952

[21] van Campenhout, E Nouvelles recherches au sujet des cellules sympathicotropes du testicule Comp rend Soc de biol 140 1135–1137, 1946

[22] van Campenhout, E Les cellules sympathicotropes de Berger Acta Anat , 4 73–78 1947

[23] Amelar, R D Anorchism without eunuchism J Urol 76 174–178, 1956

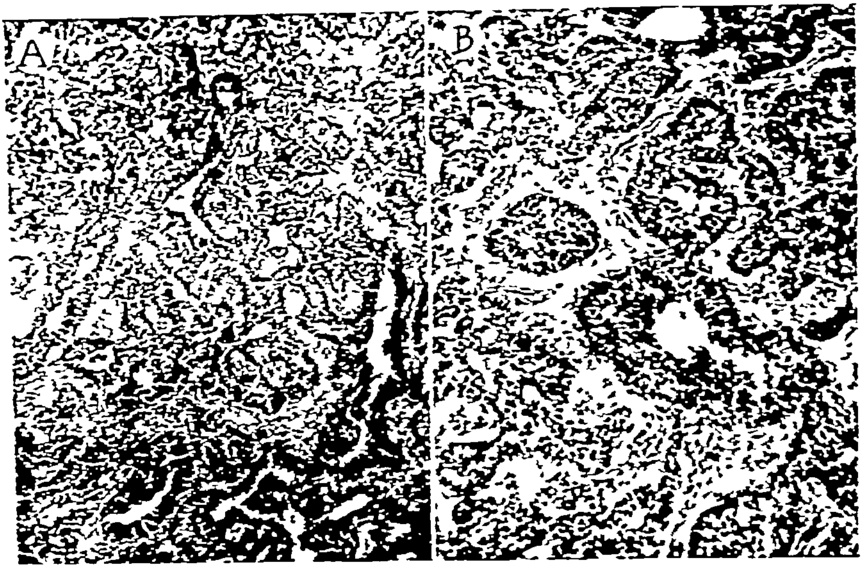

FIG 3 *A*, predominantly tubular element is observed in this section of tumor *B*, higher magnification to show structure of tubules which are well demarcated by basement membrane

eosinophil cells The stroma of the lobules was densely packed with round and polygonal cells, with a scant, lightly staining cytoplasm (fig 2, *B*) The nuclei were round or oval, showed a fine granular chromatin network, and one or two small nucleoli Mitotic figures were observed occasionally throughout A definitely tubular pattern was present in some areas (fig 3) The tubules had a definite basement membrane, and were lined by one or more layers of cuboidal epithelial cells Shedding of epithelial cells into the lumen of some of the tubules was noted A pale-staining eosinophilic amorphous material was occasionally present in the larger tubules While the stromal and tubular elements were distinct, gradations between the two were also seen with arrangements of the cells into cords and pseudo-tubules Leydig-like cells with vacuoles or a foamy cytoplasm were also present Frozen sections stained with Sudan 3 showed the presence of fat in the Leydig cells

DISCUSSION

The term, androblastoma was first introduced by Teilum[1] for tumors of the testicle homologous to arrhenoblastomas (Meyer)[2] of the ovary According to Friedman and Moore,[3] they constitute 0 4 per cent of testicular tumors They are tumors originating from a testicular blastoma in which a differentiation necrosis or hemorrhage were observed The cord, though somewhat thickened, and the epididymis were within normal limits

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[1] Teilum, G Arrhenoblastoma—androblastoma homologous ovarian and testicular tumors, including the so-called "luteomas" and adrenal tumors" of ovary and interstitial cell tumors of testis Acta Path et Microbiol Scandinav , 23 252-64, 1946

[2] Meyer R Tubuläre (testiculäre) und solide Formen der Andreiblastoma ovarii und ihre Beziehung zur Vermännlichung Beitr z Path Anat u.z allg Path , 84 485-520, 1930

[3] Friedman N B and Moore R A Tumors of the testis A report of 922 cases Military Surg 99 573-93 1946

Microscopically, the sections showed a somewhat thickened tunica vaginalis Immediately subjacent to the tunica albuginea some compressed tubules, otherwise without note, were observed (fig 2, *A*) Occupying the place of the normal testicle was a well-encapsulated tumor, partitioned into lobules by fibrous connective tissue septa, and infiltrated with some lymphocytes, polymorphs and

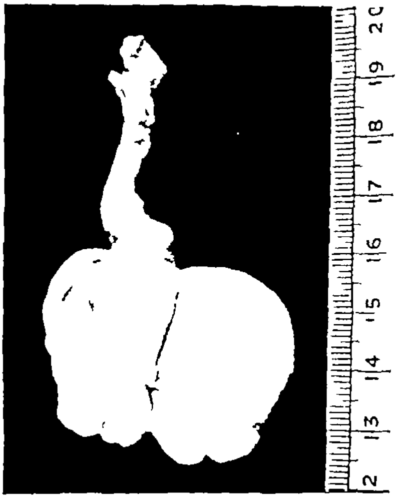


FIG 1 Gross specimen removed by operation

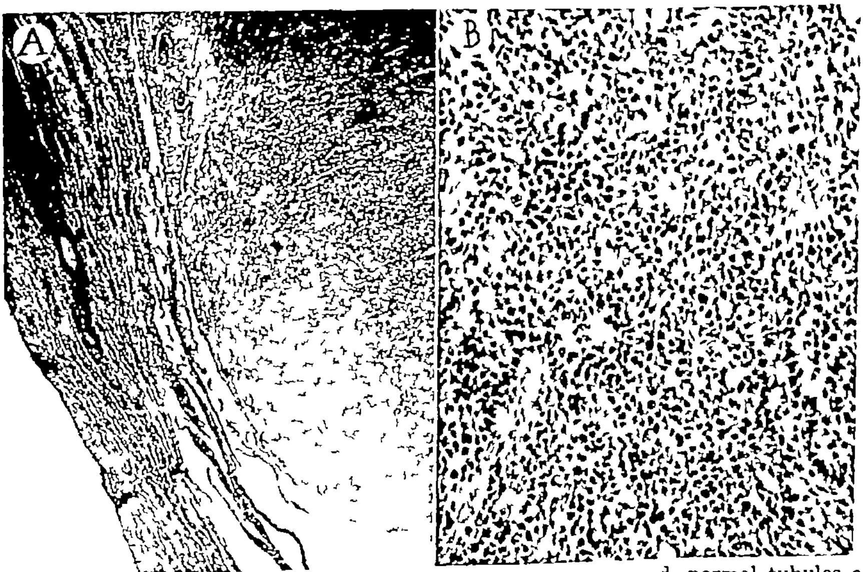
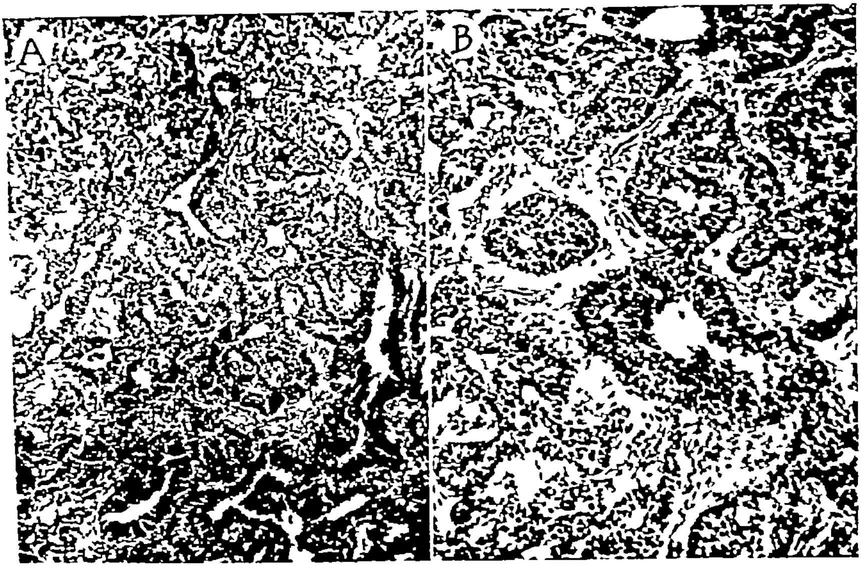


FIG 2 *A*, tumor seen to be well encapsulated Few compressed, normal tubules are noted between collagen bundles (low magnification) *B*, predominantly stromal element is present here, though occasional attempts at formation of lumina can be seen



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DISCUSSION

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[1] Teilum, G Arrhenoblastoma—androblastoma, homologous ovarian and testicular tumors, including the so called "luteomas" and 'adrenal tumors" of ovary and interstitial cell tumors of testis Acta Path et Microbiol Scandinav , 23 252-64, 1946

[2] Meyer R Tubuläre (testiculäre) und solide Formen der Andreiblastoma ovarii und ihre Beziehung zur Vermännlichung Beitr z Path Anat u z allg Path , 84 485-520, 1930

[3] Friedman, N B and Moore, R A Tumors of the testis A report of 922 cases Military Surg 99 573-93, 1946

To our knowledge only six diffuse and mixed androblastomas, three of Teilum,[1, 4] and three of Freidman and Moore,[3] have been reported, to which cases we are adding a seventh The age incidence of the published cases varied from 4 to 52 years Our case of an infant aged 3½ months is the youngest so far reported

The arrhenoblastomas of the ovary produce virilizing effects in females, while the homologous androblastomas in the male are sometimes associated with feminizing effects *According to Teilum,*[1, 4, 7] *this apparently paradoxical behavior* depends on the predominance of either lipoidal androgen-producing Leydig cells (stromal element), or of estrogen-producing Sertoli cells (tubular epithelial element) Of the six reported cases referred to above, only one (Teilum's) was associated with hormonal effects, viz, gynecomastia Our patient did not show any signs of hormonal disturbance, though admittedly, hormonal assays were not performed

None of the reported cases was malignant, although as Dixon and Moore[6] point out, the possibility exists of malignant variants of androblastoma as indicated by the not infrequent occurrence of malignant arrhenoblastomas

SUMMARY

The history and clinical picture of a case of androblastoma of the left testis in an infant 3½ months old are described The tumor presented as a painless swelling of the left side of the scrotum of 1 month's duration prior to admission Signs of hormonal imbalance were absent

A left orchiectomy was performed, the child remaining alive and well until the present time

The gross and microscopic findings are described The tumor was of the mixed type of androblastoma, with the presence of both tubular and diffuse stromal elements

A brief comment is made on the reported cases of androblastoma in the literature

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[4] Teilum, G Estrogen producing *Sertoli cell* tumors *(androblastoma tubulare lipoides)* of the human testis and ovary Homologous ovarian and testicular tumors III J Clin Endocrinol, 9 301-18, 1949

[5] Pick, L Ueber Neubildungen am Genitale bei Zwittern nebst Beiträgen zur Lehre *von den Adenomen des Hodens und Eierstockes* Arch f Gynäk, 76 191-281, 1905

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EFFECTS OF L-THYROXINE AND LIOTHYRONINE ON SPERMATOGENESIS

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Thyroxine (3,5,3',5'-tetraiodothyronine) and liothyronine (3,5,3'-triiodothyronine) are the active principles of the thyroid hormone. Liothyronine is more active than thyroxine in that a given dose has a more rapid onset of action and produces a greater rise in oxygen consumption. However, the action of thyroxine is much more sustained.[1]

Like the natural hormone, desiccated thyroid or thyroglobulin, thyroxine and liothyronine may be used for replacement therapy of diminished or absent thyroid function and they may be useful in a variety of acute and chronic disorders including female infertility. They differ, however, in their effects on male infertility: desiccated thyroid and thyroglobulin produce no significant changes in semen while L-thyroxine and liothyronine may affect spermatogenesis.[2] This report relates some of the different ways in which L-thyroxine and liothyronine (cytomel) may affect the semen of subfertile and relatively fertile men.

METHOD

Twenty-six men with fertility problems were selected at random for this evaluation. Each man received two or more semen analyses before being included in the group. For each analysis, semen was collected after the patient had been abstinent for at least 5 days. The volume of ejaculate was measured and counts were made of the number and percentage of forward moving cells. Normal speed was considered to be an average time of 0.7 to 1.2 seconds for 25 sperm to travel $\frac{1}{20}$ mm. (one square of an erythrocyte chamber). A patient with a total count of more than 185 million active sperm was classed as highly fertile,[3] between 80 and 185 million was called relatively fertile, and fewer than 80 million was called subfertile.[2]

On the basis of these criteria, 21 men in this series were classed as subfertile, five, relatively fertile.

Five relatively fertile men and nine subfertile men received L-thyroxine and liothyronine in separate trials 5 to 6 months apart. One subfertile man received only L-thyroxine therapy and 11 subfertile men received liothyronine therapy. The maximum doses of L-thyroxine and liothyronine used were approximately equivalent in calorigenic activity.

L-thyroxine was given 0.1 mg. daily for two weeks and 0.2 mg. daily for four weeks. At the end of the six weeks, medication was stopped. Semen analyses

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This study was aided by a grant from the Samuel S. Fels Fund and by the thoughtful assistance of Charles Parmenter, Ph.D., Werner Vandenberg and Martin Sampson.

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[2] Farris, E. J.: Advances in the treatment of sterility. Ann. Rev. Med., 7: 97–108, 1956.

[3] Farris, E. J.: Human Fertility and Problems of the Male. Palisades Park, N. J.: The Author's Press, 1950.

were made after 2, 4, and 6 weeks of medication and 2, 6, and 10 weeks after medication was stopped

Liothyronine therapy was started at a daily dose of 5 mcg , and increased at 2-week intervals to 12 5 mcg , 25 mcg and 50 mcg daily After two weeks on each dosage, semen analyses were made

RESULTS

L-thyroxine therapy Subfertile men As shown in figure 1, the 10 subfertile men who received L-thyroxine had increases in the total number of sperm cells but marked decreases in the per cent of the cells which were active and in the speed of their forward movement

After therapy was discontinued the number of cells fell below pretreatment levels The speed of the sperm continued to show a marked depression and, in 5 patients, all forward movement of the sperm ceased Ten weeks after medication was stopped, all factors returned to approximately their pretreatment levels

Relatively fertile men As shown in figure 2, on L-thyroxine therapy the 5

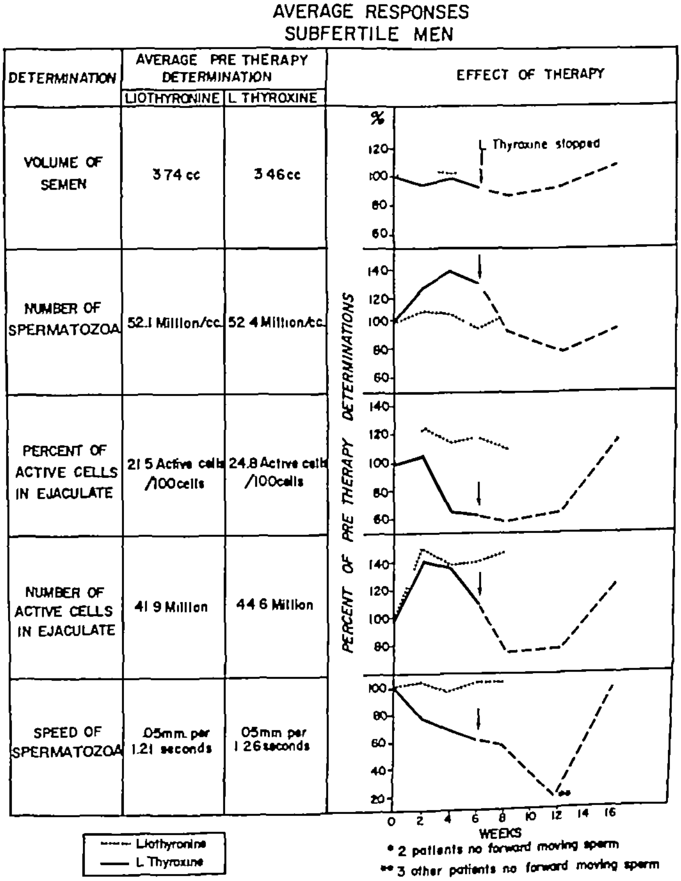

Fig 1

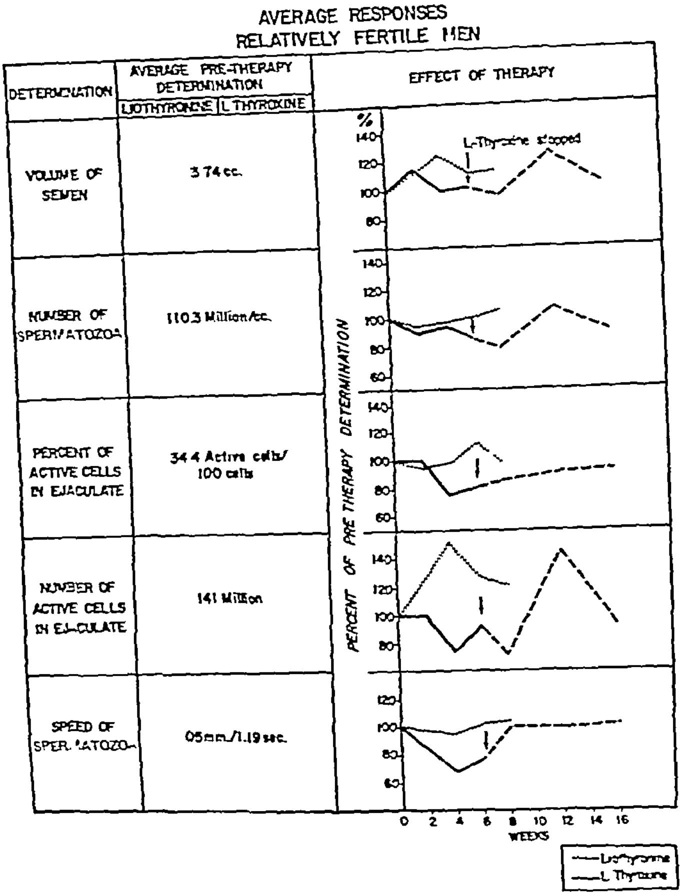

FIG 2

relatively fertile men showed decreases in number and percentage of active cells Moreover, the speed of the active cells fell markedly

Two weeks after medication was stopped, there were decreases in the number of cells and in the percentage of active cells in the ejaculate The speed of the cells returned to control levels Six weeks after medication was stopped the volume of semen and the total number of cells increased beyond pretreatment levels However, there was no increase in the speed of the active cells By ten weeks after medication was stopped, all factors had returned to approximately pretreatment levels

Liothyronine therapy Subfertile men As shown in figure 1, on the whole, the subfertile men treated with liothyronine responded well at all doses of medication Patients showed some increase in volume of semen and in total number of cells They showed a marked increase in percentage of active cells but little change in speed of activity

Fourteen of the 20 subfertile men treated with liothyronine showed increases in number and speed of active cells seven improved sufficiently to be reclassed were made after 2, 4, and 6 weeks of medication and 2, 6, and 10 weeks after medication was stopped

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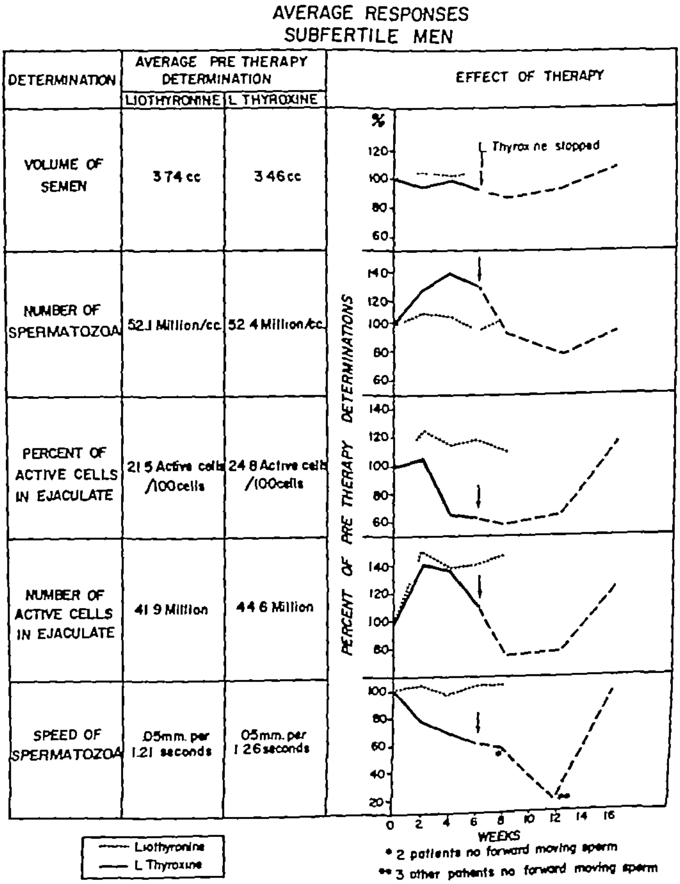

FIG 1

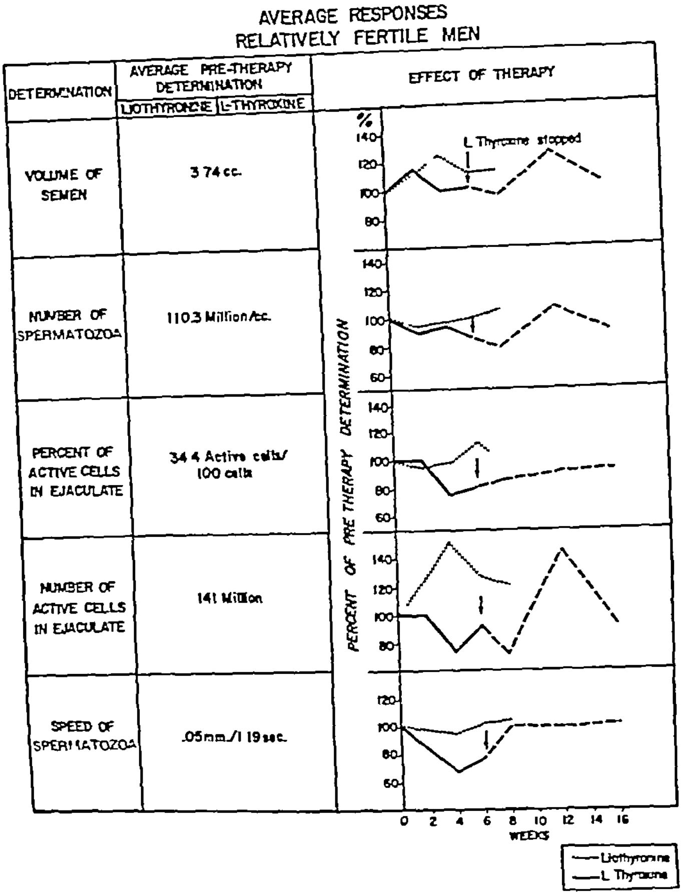

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TABLE 1 *Comparisons of speed of spermatozoa in response to therapies*

Medication	Daily Dose	Average Speed of Sperm (seconds per 1/20 mm)	Change
9 Subfertile Men			
Control	—	1 3	—
L thyroxine	0 1 mg	1 6	0 3 seconds slower
	0 2 mg	1 9	0 6 seconds slower
Liothyronine	25 mcg	1 3	no change
	50 mcg	1 2	0 1 second faster
5 Relatively Fertile Men			
Control	—	1 2	—
L thyroxine	0 1 mg	1 4	0 2 seconds slower
	0 2 mg	1 8	0 6 seconds slower
Liothyronine	25 mcg	1 2	no change
	50 mcg	1 1	0 1 second faster

as relatively fertile and seven improved to a lesser extent The sperm counts of 5 patients showed no essential changes and those of one man were consistently worse Wives of 5 patients became pregnant during the evaluation

Relatively fertile men As shown in figure 2, at all dosages of liothyronine the five relatively fertile men had increased in the volume of their semen and in the number of active cells The total number of sperm cells and the speed of the active cells remained essentially unchanged

Comparative results There were important differences in the responses to therapy with L-thyroxine and liothyronine in the 14 patients who received both medications As shown in table 1, on L-thyroxine, the speed of the spermatozoa decreased considerably, on liothyronine, the speed of the cells did not change significantly Furthermore, the average percentage of active sperm in the ejaculate was increased to a greater extent by liothyronine than by L-thyroxine In the subfertile men, on 0 2 mg of L-thyroxine the average percentage of active sperm decreased by 12 1 per cent from pretherapy levels, on 50 mcg of liothyronine the percentage of active sperm increased by 2 9 per cent In the relatively fertile men, there was a decrease of 7 5 per cent on 0 2 mg of L-thyroxine and a decrease of 1 3 per cent on 50 mcg of liothyronine

DISCUSSION

The results of this investigation are interesting because *they show that directly or indirectly the thyroid hormonal factors* have a profound effect upon spermatogenesis The results show too that the nature of the effect depends upon the thyroid factor involved—L-thyroxine, or liothyronine

Differences in action *between liothyronine and thyroid* hormone have often been noted[4 7] and various investigators have found that patients refractory to

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desiccated thyroid and other thyroid products may respond to therapy with liothyronine[8] [9] In this evaluation, the differences in action were striking therapy with L-thyroxine decreased sperm motility and in some cases destroyed it completely, in contrast, therapy with liothyronine increased potential fertility by increasing the number of active sperm without decreasing the speed of their movement

A discussion of the many and involved relations in the endocrine system through which these differences in effect upon spermatogenesis may be produced is beyond the scope of this paper It is apparent, however, that a great deal of research remains to be done before we can offer sound endocrine aid to the subfertile or relatively fertile male

SUMMARY AND CONCLUSIONS

Five relatively fertile men and 21 subfertile men were treated in this evaluation of L-thyroxine and liothyronine (cytomel) The maximum dosage of L-thyroxine was 0 2 mg daily and of liothyronine was 50 mcg daily These doses are approximately equivalent on the basis of calorigenic activity Semen analyses showed that the subfertile and relatively fertile men who received L-thyroxine had decreases in the percentage of active cells in the ejaculate and marked decreases in the speed of the cells After L-thyroxine therapy was discontinued, the sperm of half the subfertile men temporarily lost all forward movement It took about 10 weeks before activity was recovered Sperm of relatively fertile men also decreased in activity when L-thyroxine therapy was stopped, but recovered more rapidly

Subfertile and relatively fertile men who received liothyronine therapy showed increases in the number of cells and in the percentage of active cells in their ejaculate The speed of the cells was unchanged in the relatively fertile and subfertile men Seven of the subfertile men (35 per cent) improved sufficiently to be reclassed as relatively fertile Seven others improved to a lesser extent, five showed no change, and one was consistently worse Wives of five subfertile men became pregnant during the test of liothyronine therapy

Comparison of the effects of L-thyroxine and liothyronine in equivalent doses and in the same subfertile and relatively fertile men revealed that patients had a marked depression in the speed of spermatozoa when treated with L-thyroxine and either had no change or improved when treated with liothyronine

In this evaluation, L-thyroxine appeared to hinder the chances for conception while liothyronine may have enhanced them

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MALE SUBFERTILITY TREATMENT WITH LIOTHYRONINE (CYTOMEL)

D CRAMER REED, WILLIAM H BROWNING AND HAROLD F O'DONNELL

In 1951, Gross and Pitt-Rivers isolated a substance from the plasma of normal and hyperthyroid patients that was not present in the plasma of hypothyroid patients In 1952 the substance was identified as 3,5,3′ L-triiodothyronine (liothyronine) In chemical structure liothyronine differs from L-thyroxine by the absence of one iodine atom It has been suggested that liothyronine may be the ultimate thyroid hormone, and that L-thyroxine becomes effective at the cellular level through de-iodination to the liothyronine form[1, 2]

Although liothyronine is related to thyroxine, it has somewhat different biological effects It is considerably more active and has a faster onset and cut-off of activity For this reason, the dosage of liothyronine can readily be adjusted and therapy can be discontinued without the tapering-off period required by thyroid hormones The drug has been used successfully for treating a number of disorders including hypothyroidism and simple (non-toxic) goiter[3, 4]

Recently, Farris[5] reported that liothyronine increased the number and speed of spermatoza in subfertile men His findings on 16 patients prompted this investigation in a larger series to evaluate liothyronine therapy for improving male fertility

STUDY

Forty-five men who were shown by semen analyses to be oligospermic were treated with liothyronine Semen analyses showed all patients were deficient in number or speed of spermatozoa

In determining the number of spermatoza in the ejaculate, only living, active cells with good forward motility were counted Patients with fewer than 80 million spermatozoa in their entire ejaculate were arbitrarily considered subfertile, those with 80 to 185 million were considered relatively fertile, and those with more than 185 million were considered highly fertile[6, 7]

Speed of spermatozoa was calculated using the techniques suggested by Harvey and Jackson[8] and improved upon by Farris[6] Normal speed was taken to be

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TABLE 1 *Effects of liothyronine therapy upon men treated for deficiencies in both number and speed of spermatozoa*

Patients	Number of Spermatozoa (in millions)		Speed of Spermatozoa* (in seconds 0.05 mm.)		Comments
	Before therapy	After therapy	Before therapy	After therapy	
(Patients improved in both number and speed of spermatozoa)					
1	51	382	—	1.1	highly fertile
2	41	198	2.9	1.3	highly fertile
3	78	311	2.9	1.0	conception
4	31	277	2.4	1.0	conception
5	39	107	1.9	1.2	relatively fertile
6	53	132	2.3	1.2	relatively fertile
7	8	133	1.8	1.3	conception
8	8	128	2.0	1.2	conception
9	49	74	2.7	1.6	conception
10	37	88	2.4	1.0	conception
11	0	22	—	1.4	
12	7	17	—	1.8	
13	5	17	—	1.4	
14	18	30	—	1.1	
(Patients improved in either number or speed of spermatozoa)					
15	23	110	1.5	1.5	conception
16	66	186	4.5	4.5	
17	9	29	2.0	2.0	
18	5	15	—	—	
19	5	15	1.9	1.9	
20	19	22	—	2.4	
21	45	43	1.3	1.1	
22	32	37	1.6	1.5	
23	20	13	1.8	1.3	
24	27	20	—	1.6	
(Patients unaffected by therapy)					
25	16	11	—	—	
26	4	4	—	—	
27	0	0	—	—	
28	17	11	—	—	
(Patients adversely affected by therapy)					
29	71	49	1.5	1.5	
30	11	2	1.4	2.6	
31	46	8	1.7	1.9	
32	42	13	1.8	2.6	

* (—) means fewer than 25 moving spermatozoa per 0.05 mm.

an average time of from 0.7 to 1.2 seconds for 25 or more forward moving spermatozoa to cross one square (0.05 mm.) of an erythrocyte chamber

Thirty-two patients had deficiencies in both number and speed of spermatozoa. These patients had fewer than 80 million active cells with an average

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MALE SUBFERTILITY TREATMENT WITH LIOTHYRONINE (CYTOMEL)

D CRAMER REED, WILLIAM H BROWNING AND HAROLD F O'DONNELL

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Recently, Farris[5] reported that liothyronine increased the number and speed of spermatoza in subfertile men His findings on 16 patients prompted this investigation in a larger series to evaluate liothyronine therapy for improving male fertility

STUDY

Forty-five men who were shown by semen analyses to be oligospermic were treated with liothyronine Semen analyses showed all patients were deficient in number or speed of spermatozoa

In determining the number of spermatoza in the ejaculate, only living, active cells with good forward motility were counted Patients with fewer than 80 million spermatozoa in their entire ejaculate were arbitrarily considered subfertile, those with 80 to 185 million were considered relatively fertile, and those with more than 185 million were considered highly fertile [6, 7]

Speed of spermatozoa was calculated using the techniques suggested by Harvey and Jackson[8] and improved upon by Farris [6] Normal speed was taken to be

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[8] Harvey, C and Jackson, M H Assessment of male fertility by semen analysis Lancet, **2** 99–105, 1945

improve the speed of their spermatozoa Six failed to benefit—showing no appreciable increase or a slight decrease

Although all 45 patients were classed as subfertile before therapy, 12 men improved sufficiently to be reclassed as relatively fertile, and 6 men improved to the extent that they could be called highly fertile Conceptions were reported among the wives of 8 of the 18 fertile men On the basis of semen analyses it was not possible to differentiate between the men whose wives became pregnant and those whose wives did not

There was no detectable correlation between duration of liothyronine therapy and the therapeutic responses Most patients responded to a daily dose of 12 5 mcg or 15 mcg (the maximum dose given) In only one case did therapy produce any untoward effect This consisted of increased pulse rate associated with symptoms of nervousness which subsided when the drug was discontinued

DISCUSSION

It is exceedingly difficult to judge the value of therapy for improving male fertility because there are many factors which must be considered At the very least, a therapy for treating oligospermic patients should increase both the total number and the motility of the spermatozoa A therapy which increases the number of cells per cubic centimeter by reducing the quantity of the ejaculate is of doubtful value Also doubtful is a therapy which increases activity of the cells but decreases their number For these reasons, in this evaluation of liothyronine, therapeutic efficacy was judged by changes in the number of normal forward moving spermatozoa in the entire ejaculate and by changes in the average speed of the spermatozoa

Using these criteria, the majority (69 per cent) of subfertile, oligospermic men were benefited by liothyronine therapy This finding supports that of Farris[5] that liothyronine appears of value in treating subfertile men In some patients, however, the value of the increases in number and speed of spermatozoa was questionable Patient 11 (table 1), for example, improved from no active spermatozoa with forward motility before therapy to 22 million active spermatozoa with an average speed of 1 4 seconds/0 05 mm after therapy The improvement is important, but the patient must still be considered subfertile based on the criteria used by our group It is entirely possible however, that with continued treatment, and with doses of liothyronine higher than 15 mcg, patient number 11, and the others who showed suboptimal responses, might have improved to the extent of becoming fertile Even on small doses of liothyronine, 18 subfertile patients became relatively fertile and even highly fertile

SUMMARY AND CONCLUSIONS

Forty-five subfertile, oligospermic men were treated with liothyronine (cytomel) for from 3 to 26 weeks The maximum dose given was 15 mcg daily Almost 70 per cent of the men showed increases in the number of spermatozoa in their entire ejaculate, in the speed of the spermatozoa, or in both number

TABLE 2. *Effects of liothyronine therapy upon men treated for deficiencies in either number or speed of spermatozoa*

Patients	Number of Spermatozoa (in millions)		Speed of Spermatozoa* (in seconds/0.05 mm.)		Comments
	Before therapy	After therapy	Before therapy	After therapy	
(Patients treated for deficiencies in number)					
33	40	115	1.2	1.1	Relatively fertile
34	43	83	1.1	1.1	Relatively fertile
35	25	113	1.2	1.6	Relatively fertile?
36	70	112	1.1	1.6	Relatively fertile?
37	28	32	0.9	1.3	
38	3	3	1.0	—	
39	31	23	1.1	1.7	
40	41	25	1.1	1.4	
41	75	45	1.2	1.5	
42	25	10	1.2	—	
(Patients treated for deficiencies in speed)					
43	92	372	2.5	1.1	Highly fertile
44	95	181	2.8	1.3	Conception
45	87	79	1.4	1.0	Relatively fertile

* (—) means fewer than 25 moving spermatozoa per 0.05 mm.

speed of less than 1.2 seconds/0.05 mm. Thirteen patients had deficiencies in either number or speed of spermatozoa (tables 1 and 2). All 45 patients were classed as subfertile.

Patients were treated with liothyronine for from 3 to 26 weeks. Medication was begun as one 5 mcg. tablet each day and, depending upon the individual's response, was increased gradually to a maximum of 15 mcg. daily.

Semen analyses were made on all patients before therapy and then periodically as long as medication was given. Each analysis was made after the patient had been abstinent for 5 days.

At each visit, patients were questioned about side effects, and changes in their semen were noted. A significant change in semen was considered to be an increase or decrease of 10 million or more in number of spermatozoa or of 0.1 second/0.05 mm. or more in speed of spermatozoa.

RESULTS

As shown in table 1, 24 of the 32 men treated for deficiencies in both number and speed of spermatozoa improved under therapy. Fourteen of these men improved in both factors, while 10 men improved in one factor with no significant change in the other. Four men showed no significant change in either number or speed of spermatozoa; 4 men showed a decrease.

As shown in table 2, 13 men were treated for deficiencies in either number or speed of spermatozoa. Therapy benefited 4 patients who were treated to improve the number of their spermatozoa and 3 patients who were treated to

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RETROPUBIC BIOPSY OF THE PROSTATE

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Since prostatic calculi and inflammatory lesions of the prostate may simulate the rectal palpatory characteristics of carcinoma of the prostate, it is usually necessary to obtain a biopsy of the gland before proper therapy can be instituted Several methods have been devised whereby representative pieces of tissue can be removed for microscopic examination (fig 1) Each of these techniques has advantages and disadvantages which render them more or less applicable under certain conditions (table 1) In order to understand the need for retropubic biopsy of the prostate, a distinction between total and radical prostatectomy must be made A total prostatectomy connotes excision of the prostate and seminal vesicles and can be accomplished by either a perineal or retropubic exposure Radical prostatectomy, on the other hand, includes an excision of the regional lymphatic channels and lymph nodes along with the prostate and seminal

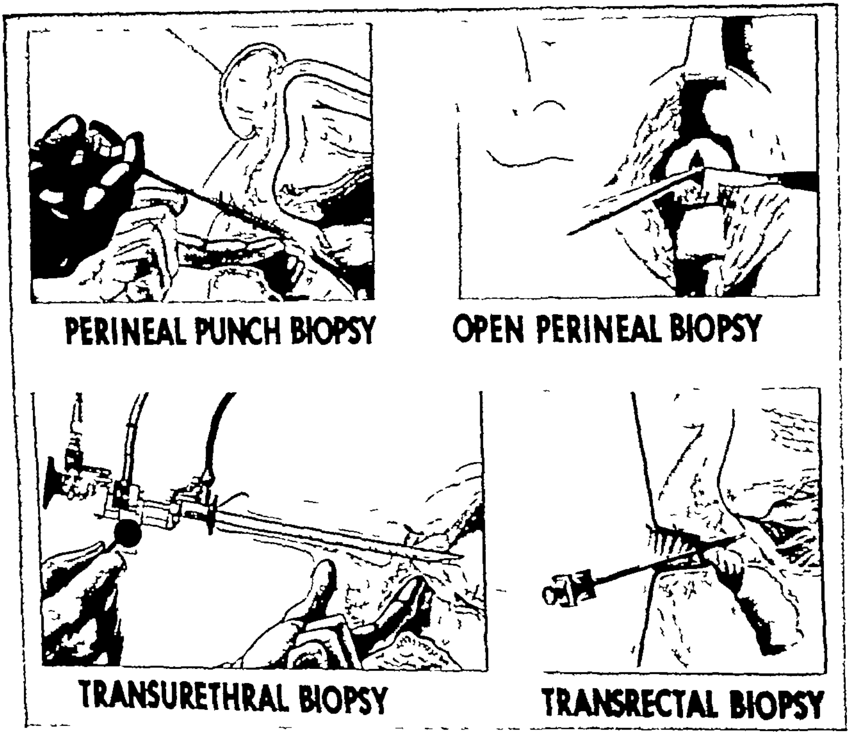

PERINEAL PUNCH BIOPSY
OPEN PERINEAL BIOPSY
TRANSURETHRAL BIOPSY
TRANSRECTAL BIOPSY

FIG 1

Read at annual meeting of North Central Section of American Urological Association, Mackinac Island, Mich , August 29-31, 1957

and speed Eighteen men improved markedly under liothyronine therapy and could be reclassified as relatively fertile or even highly fertile Wives of 8 of these 18 men conceived

There was no detectable correlation between the duration of therapy and the therapeutic responses Only one of the men reported undesirable effects

The good responses observed in this clinical evaluation of liothyronine therapy to improve male fertility suggest that this use of the drug deserves further research

427 N Hillside, Wichita, Kans

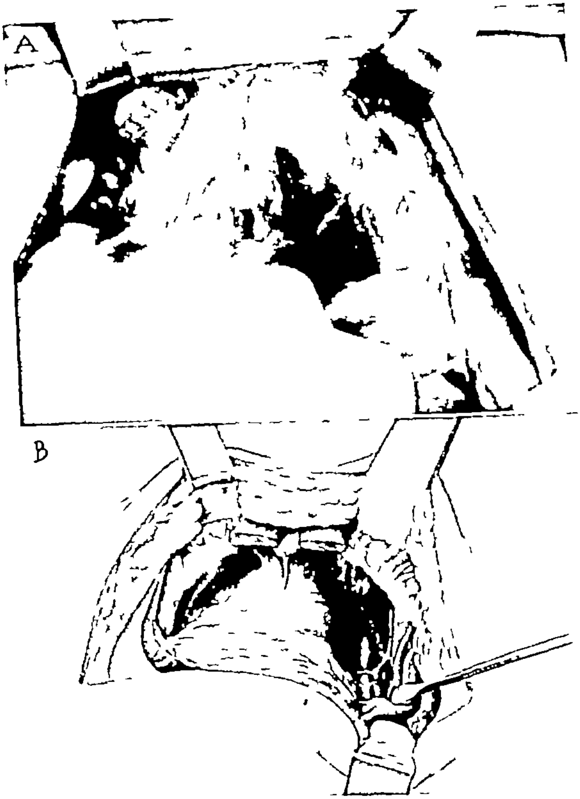


Fig 2

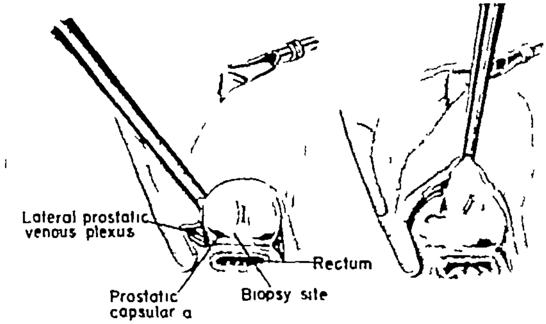


Fig 3

wall with a sharp pointed hemostat (fig 3) With this fascia opened, the rectum is easily identified as a soft bulging structure lying deep to the more compact, firm prostate By blunt dissection with the finger, the prostate is separated from the rectum utilizing the cleavage plane between the layers of Denonvilliers' fascia After this has been accomplished bilaterally, the entire posterior surface of the prostate is freed from the rectum so that the prostate remains attached only to

TABLE 1

Type of Biopsy	Advantages	Disadvantages
Perineal needle	No incision Minor procedure Early ambulation No interference with subsequent procedures	Negative result meaningless—75% accuracy Small sized pieces of tissue difficult to examine Hematuria—rare
Open perineal	Large, easy to examine specimen Accurate identification of suspicious area Routine biopsy of posterior lobe when performing perineal partial prostatectomy Proceed immediately with total prostatectomy if positive diagnosis is established	If permanent sections are necessary, a second operative procedure is required Difficulty in placing the patient
Transurethral	Relief of bladder neck obstruction at same time	Poor approach to carcinoma which generally arises in posterior lobe
Transrectal—needle	Easy direct access to suspicious area Minor procedure No incision Early ambulation Does not interfere with subsequent procedures	Prostatitis Hematuria—rare

vesicles and can only be accomplished by a retropubic exposure Under these conditions it would be necessary to subject the patient to either two separate operative procedures or considerably prolonged single procedure because of the necessity of changing the patient's position on the operating room table after the biopsy Therefore, a technique to obtain an adequate biopsy for frozen section by the retropubic approach was devised

TECHNIQUE

The prostate gland is exposed through a curved, lower abdominal incision which is carried through the fascia and fibers of the rectus muscle If the abdominal wall is thick and the pelvis is deep, additional exposure can be obtained by incising the lateral abdominal muscles After the lateral periprostatic and retropubic areas have been developed by sweeping away the areolar and fatty tissue, the endopelvic fascia which passes over the prostate to the lateral pelvic walls is identified (fig 2) In order to avoid the lateral prostatic venous plexus the fascia is opened midway between the lateral border of the prostate and pelvic

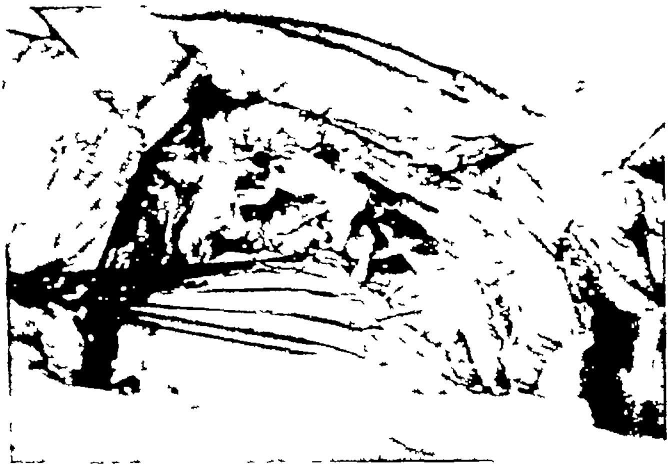


FIG 6

the membranous urethra at its apex and the bladder neck at its base With aid of retractors to depress the rectum, and traction on the lateral border of the prostate the posterior surface can be rotated into view first on one side and then on the other (fig 4, A) Adequate sections of tissue can then be removed from any desired point (fig 4, *B* and 5)

While the pathologist examines the tissue by frozen section, the internal iliac, external iliac and periaortic lymphatic channels and lymph nodes are inspected for gross neoplastic invasion. Depending upon the pathologist's report and the extent of the lesion, one can then proceed with whatever procedure is indicated

If the microscopic examination of the excised tissue reveals no evidence of neoplastic change, the site of the biopsy is closed with several interrupted sutures of size 1 chromic catgut (fig 6) Drains are placed in the periprostatic areas and the wound is closed by re-approximating the fibers and fascia of the abdominal musculature with interrupted size 1 chromic catgut, the subcutaneous tissue with plain 0 catgut and the skin with 000 silk sutures

SUMMARY

A technique for retropubic biopsy of the prostate gland has been presented which exposes the entire posterior surface of the prostate and permits biopsy of any desired site

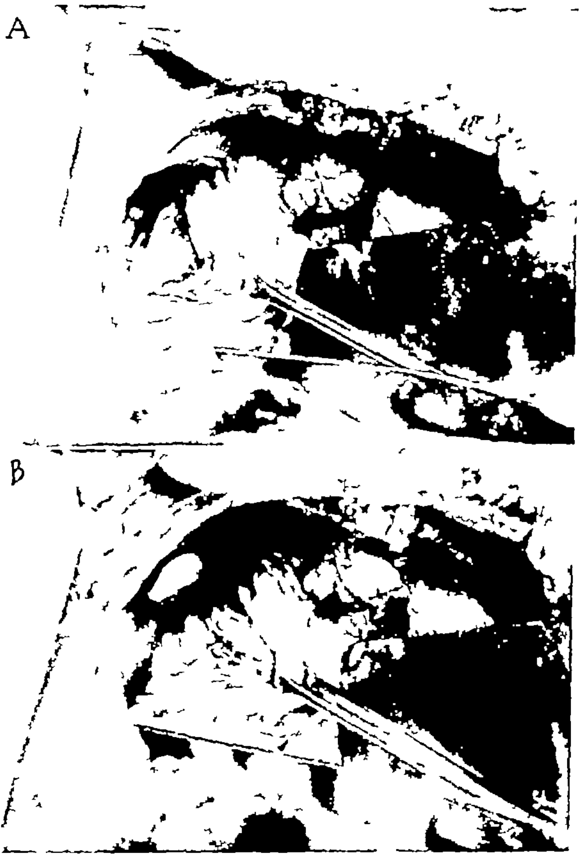
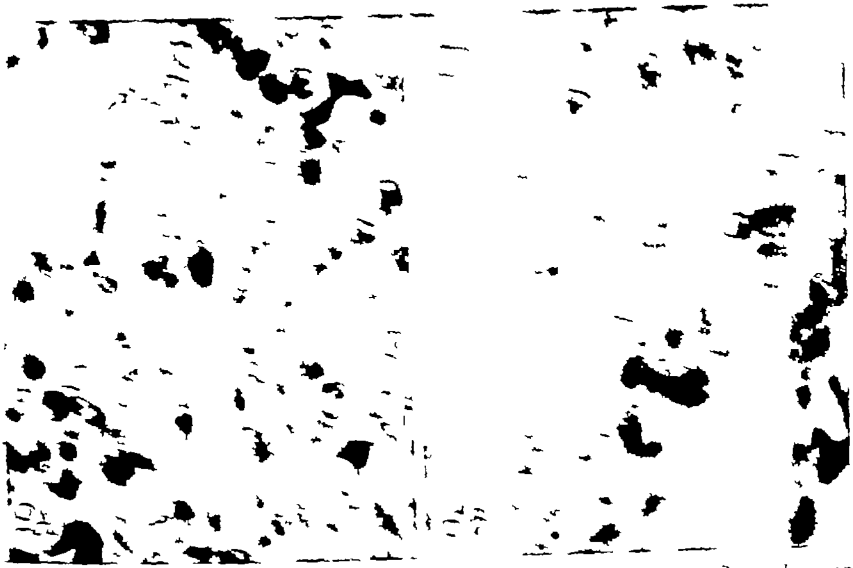


FIG 4

FIG 5



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MATERIALS AND METHODS

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CHROMOSOMAL SEX DETERMINATION OF THE PROSTATE

HAROLD G KUDISH AND HARRY M BAUER

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It is the purpose of this paper to present data on the incidence of sex chromatin in epithelium of prostatic hyperplasia and prostatic cancer There is a sex difference in the structure of the nucleus, based on the more conspicuous sex chromatin of the female, present in all types of cells This sex difference in nuclear morphology was first described by Barr and Bertram[1] and has subsequently been intensively investigated [2-4] On the basis of present information it is assumed that the two X chromosomes in female cells fuse to form a single mass of sex chromatin which is sufficiently large and morphologically typical to be distinguished from the more generalized particulate chromatin The sex chromatin measures 0 7 to 1 2 microns, appearing as a dense planoconvex mass adhering to the inner surface of the nuclear membrane In some nuclei sex chromatin is disc-shaped or triangular with the base of the triangle applied to the nuclear membrane (fig 1, *A*) The sex chromatin is Feulgen-positive and has a strong affinity for methyl green by virtue of its high concentration of DNA A mass of sex chromatin can be identified in approximately three-fourths of all nuclei in five micron sections of female tissue, the range being 52–89 per cent [3] Cells in smears of oral mucosa and peripheral blood possess a somewhat different, though characteristic, incidence of sex chromatin [5-7]

A chromatin mass morphologically resembling the sex chromatin of females has been found in up to 21 per cent of male nuclei The average incidence for various tissues is less than 10 per cent The broad range between the upper limit recorded for males and the lower limit recorded for females serves to eliminate any difficulty in ascertaining the sex of the tissue In five cases studied by Moore and Barr[3] the incidence of sex chromatin in normal prostatic glandular epithelium ranged from 3–14 per cent with an average of 8 per cent Three cases of prostatic hyperplasia studied by these same authors showed a 6 per cent average incidence of sex chromatin [8] Studies of tumors and hyperplasias demon-

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10 per cent as female[11] This simple but important difference in criteria is alone sufficient to explain their results

SUMMARY

The nuclear morphology of prostatic epithelium was studied in 125 cases of benign hyperplasia and 50 cases of adenocarcinoma The incidence of sex chromatin was within the accepted male range in all cases

No significant difference in the incidence of sex chromatin was found in the two groups

No basis for the concept of tumor contrasex in the prostate was found

This study emphasizes the importance of adhering to established criteria for sex determination

435 North Roxbury Drive, Beverly Hills, Calif

stained with hematoxylin and eosin were examined under oil immersion (X 970) Previous experience with a wide variety of tissues by one of us (H M B) has established the validity of this method Seventy-eight cases were eliminated because sections failed to meet technical requirements for fine nuclear details Pyknosis, hyperchromatism, clumped chromatin and overstaining were the grounds for rejection For the most part this was due to artefacts of cauterization in transurethrally resected material

RESULTS

In the 175 cases comprising the final study there were 125 cases of hyperplasia and 50 cases of carcinoma The incidence of nuclear sex chromatin was comparable in the two groups (table 1) The figures ranged from 0–11 per cent with an average of 3 7 per cent in hyperplasia, and from 0–15 per cent with an average of 3 2 per cent in prostatic cancer In both groups the incidence of sex chromatin is characteristic of the male sex

DISCUSSION

This study contradicts the previously mentioned work of Coutts, et al The explanation for this contradiction is found in the criteria for sex differentiation (fig 2) Moore and Barr[3, 4] found a range of sex chromatin in male tissues from 1–21 per cent with an average of 7 4 per cent On the other hand, the incidence of sex chromatin in females ranged from 52–89 per cent with an average of approximately 75 per cent It is apparent that there is a large intermediate range between 21 per cent and 52 per cent It is significant that in a study of adequate material counts in this intermediate range are not encountered[3, 4] Coutts and his co-workers ignore this broad range They arbitrarily regard an incidence of less than 10 per cent as indicative of male sex, and anything above

TABLE 1 *Incidence of nuclear sex chromatin in epithelium of prostate*

Type of Tissue	Range	Average
Hyperplasia, 125 cases	0–11%	3 7%
Carcinoma, 50 cases	0–15%	3 2%

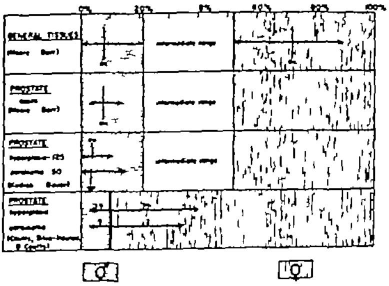

FIG 2 Incidence of nuclear sex chromatin in general tissues and in prostatic epithelium to illustrate criteria for sex determination

heart infusion blood broth was also inoculated The original urine was also incubated In case no growth was obtained from the cultures, the incubated urine was plated again on the media mentioned Novobiocin was then administered in 500 mg doses, four times daily after meals, on a full stomach, for a maximum of ten days The drug was never given on an empty stomach Probably this is the reason why these patients did not have many gastrointestinal side effects Ten patients received 250 mg four times daily but the results were not as good as with 500 mg four times daily

In 19 patients, daily blood serum levels were measured from the second to the fifth day In other patients, blood levels were determined either on the second or third day of chemotherapy Blood counts, urine examinations and blood urea determinations were performed on patients who had elevated levels of blood urea nitrogen Routine urine cultures were taken following the treatment or discharge of the patients All patients were carefully checked for gastrointestinal disturbances, skin rashes and other toxic manifestations There were 40 males and 20 females, and their ages ranged from 4 months to 90 years Only two children were included in this series Many varieties of genitourinary conditions were represented

Practically all patients had had previous antibiotic or chemotherapy, but had failed to respond Many had other therapeutic agents administered following failure of novobiocin

The number of organisms obtained before therapy ranged from one to four types, and the post treatment cultures ranged from no growth to five types of micro-organisms

Table 1 shows in tabular form the initials, unit number, sex, age, clinical diagnosis, dose of novobiocin culture of the urine before therapy, culture of urine after therapy and blood novobiocin level in 60 patients treated with this drug

Table 2 shows the effect of novobiocin therapy on cultures obtained before and after treatment There were 18 patients who had A aerogenes in their urine before treatment, and 21 patients had positive cultures after treatment Five of the 18 cases showed no A aerogenes in their urine following the treatment On the other hand, 8 patients who did not have A aerogenes on admission showed positive urine cultures for this organism following novobiocin treatment Apparently they may have acquired this organism later on, or old infections may have relapsed There were also 29 cultures of Streptococcus faecalis before and 13 after treatment Three patients had no growth of organisms on culture by the time they were admitted to the hospital, but following treatment, their urine cultures were found to be positive In 11 of 60 cases, the urine was free of micro-organisms following treatment These included one each of E coli, and A aerogenes three of S faecalis and diphtheroids, four of B proteus and five of M pyogenes aureus

In acute urinary tract infections, the criterion of cure is very simple, but in chronic infections with surgical complications such as calculus disease strictures, hypertrophy of the prostate, carcinoma, hydronephrosis etc, the criterion of

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THE PLACE OF NOVOBIOCIN IN GENITOURINARY TRACT INFECTIONS

HARRY SENECA, JOHN K LATTIMER AND ANASTASIA JOHNSON

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Novobiocin (cathomycin Merck, albamycin Upjohn) is a relatively nontoxic antibiotic, isolated by Smith and associates[1] from Streptomyces niveus and by Wallick and associates[2] from Streptomyces spheroides in 1956 Although their endproducts (novobiocin) are identical, novobiocin is apparently produced by two different species of streptomyces

This drug belongs to the erythromycin-carbomycin- oleandomycin group and is effective primarily against a gram-positive spectrum of organisms Gram-positive bacteria are inhibited in concentrations below 25 ug/ml while most Gram-negative bacteria require up to 100 ug/ml[1] The sensitivity range of Aerobacter aerogenes has been reported to be 12 5–100 ug/ml, Salmonella genus 25–100 ug/ml, Escherichia coli 12 5–100 ug/ml, Proteus 12 5–100 ug/ml, Pseudomonas aeruginosa 100 ug/ml, aerobic spore formers 1 25–5 ug/ml, Streptococcus viridans and Streptococcus faecalis 6 25–100 ug/ml, Streptococcus pyogenes 0 0625–25 ug/ml, Micrococcus pyogenes aureus 0 078–0 3125 ug/ml, corynebacteria 0 039–50 ug/ml and pneumococci 0 039–0 625 ug/ml[3, 4]

In mouse studies, novobiocin was tested against intraperitoneal injections with M pyogenes aureus, S pyogenes, D pneumoniae, P multocida, P vulgaris, P aeruginosa, S typhi as well as against an intranasal infection with Hemophilus influenzae Intraperitoneal, intramuscular and oral therapy with novobiocin protected the infected mice at nonlethal concentrations against all except P aeruginosa and S typhi[5] With these generalizations in mind, a group of 60 patients were treated at the Squier Urological Clinic at the Columbia-Presbyterian Medical Center during 1956

METHODS AND PROCEDURE

Before any medication was administered to the patients, a catheterized specimen of urine was obtained for bacteriological study The urine was plated on E M B , brain heart infusion blood agar and Simon's citrate plates Brain

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Accepted for publication October 8, 1957

[1] Smith, C G , Dietz, A , Sokølski, W T and Savage, G M Streptonivicin—a new antibiotic Ant Chem , 6 135, 1956

[2] Wallick, H , Harris, D A , Reagan, M A , Ruger, M and Woodruff, H B Discovery and antimicrobial properties of cathomycin Antibiotic Annual, 1956, p 909 New York Medical Encyclopedia

[3] Reedy, R J and Shaffer, C H , Jr In vitro sensitivity of bacteria to novobiocin, bryamycin, oleandomycin, vancomycin, amphomycin, bacitracin and synnematin B Antibiotic Annual, 1957, p 483 New York Medical Encyclopedia

[4] Frost, B M , Valiant, M E , McClelland, L , Solotorovsky, M and Cuckler, A Antimicrobial activity of cathomycin A new antibiotic Antibiotic Annual, 1956 p 918 New York Medical Encyclopedia

[5] Vervey, W F , Miller, K. and West, M K A laboratory evaluation of the chemotherapeutic properties of cathomycin Antibiotic Annual, 1956, p 924 New York Medical Encyclopedia

TABLE 1 *Continued*

Name	Unit Number	Age	Sex	Diagnosis	Treatment	Culture Before Treatment	Culture After Treatment	Maximum Blood Level
								µg/ml
H Mac	256426	90	M	B P H	(500×4) ×15	B proteus, S faecalis	P aeruginosa, A aerogenes, Strep non hemolytic	2
S P	249571	71	M	Urinary retention	(500×4) ×6	M pyogenes aureus, paracolon, Strep non hemolytic	B proteus	120
W S	762708	33	M	Polycystic kidney (rt solitary)	(500×4) ×5	A aerogenes, E coli, Strep nonhemolytic	A aerogenes, E coli, Strep nonhemolytic	20
M V	555625	54	M	Bladder calculus	(500×4) ×6	B proteus, A aerogenes	B proteus, A aerogenes	23
M S	244006	77	M	B P H, urinary retention	(250×4) ×6	No growth	A aerogenes	
R W	800267	50	F	Polycystic kidneys	(250×4) ×5	B proteus, M pyogenes aureus, S faecalis, E coli	M pyogenes aureus, E coli	8
A S	257187	29	F	Bilateral hydronephrosis	(250×4) ×6	B proteus, A aerogenes, S faecalis, E coli	B proteus, S faecalis	7
E C	822747	55	F	Bilateral hydronephrosis	(250×4) ×6	P aeruginosa, E coli	P aeruginosa, E coli	9
C A	195461	41	M	B P H, coronary	(250×4) ×5	A aerogenes, E coli, S faecalis	E coli	
I D	251365	30	M	Bilateral hydronephrosis	(500×4) ×7	M pyogenes aureus, diphtheroids	No growth	19
J K	258307	77	M	B P H, urinary retention	(250×4) ×6	M pyogenes aureus, A aerogenes	No growth	24
E D	045020	58	M	Bilateral renal calculi	(500×4) ×8	Para colon, P aeruginosa, S faecalis	A aerogenes	72
N F	256929	4 mo	F	Bladder neck stricture, bilateral hydronephrosis	(50×4) ×10	B pyocyaneus	P aeruginosa	6

cure becomes hypothetical rather than practical For the purpose of this paper, negative urine culture is the practical and objective method of determining the efficacy of novobiocin In the case of improvement, we have in mind multiple bacterial infections in a patient before treatment With novobiocin therapy, novobiocin sensitive bacteria are killed, although the urine still shows the growth

TABLE 1 *The effect of novobiocin medication on 60 patients suffering genitourinary tract infections*

Name	Unit Number	Age	Sex	Diagnosis	Treatment	Culture Before Treatment	Culture After Treatment	Maximum Blood Level
								ug/ml
W D	249032	73	M	Bladder calculus	(500×4) ×10	No growth	A aerogenes, B proteus	88
H D	250238	52	M	Urethral stricture	(500×4) ×10	G tetragenes, diphtheroids	G tetragenes, Strep non-hemolytic, M pyogenes aureus	66
S F	465018	78	M	B P H, chronic cystitis	(500×4) ×10	G tetragenes, M pyogenes aureus	E coli, diphtheroids	13
D L	102613	21	M	Neurogenic bladder	(500×4) ×8	B proteus, Strep viridans, A aerogenes	Strep viridans, A aerogenes, M pyogenes aureus, paracolon, Strep non-hemolytic	76
J G	047662	54	M	Ca bladder, hydroureter	(500×4) ×8	B proteus, G tetragenes, A aerogenes	B proteus, G tetragenes	40
B S	047289	72	M	Chronic cystitis	(500×4) ×7	A aerogenes, Strep non-hemolytic, M pyogenes aureus	A aerogenes	6
A L C	673081	13	M	Torsion of testicle	(500×4) ×7	B aeruginosa, B proteus, G tetragenes, M pyogenes aureus	M pyogenes aureus, G tetragenes	14
C M	101730	20	F	Abscess of left kidney	(500×4) ×9	P aeruginosa, B proteus, Streptococcus faecalis	P aeruginosa, B proteus, Strep non-hemolytic	9
T D	697704	75	M	B P H	(500×4) ×6	M pyogenes aureus, G tetragenes, diphtheroids	A aerogenes	74

TABLE 1 *Continued*

Name	Unit Number	Age	Sex	Diagnosis	Treatment	Culture Before Treatment	Culture After Treatment	Maximum Blood Level
								µg/ml
H Mac	256426	90	M	B P H	(500×4) ×15	B proteus, S faecalis	P aeruginosa, A aerogenes, Strep non-hemolytic	2
S P	249571	71	M	Urinary retention	(500×4) ×6	M pyogenes aureus, para colon, Strep non hemolytic	B proteus	120
W S	762708	33	M	Polycystic kidney (rt solitary)	(500×4) ×5	A aerogenes, E coli, Strep non hemolytic	A aerogenes, E coli, Strep non-hemolytic	20
M V	555625	54	M	Bladder calculus	(500×4) ×6	B proteus, A aerogenes	B proteus, A aerogenes	23
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R W	800267	50	F	Polycystic kidneys	(250×4) ×5	B proteus, M pyogenes aureus, S faecalis, E coli	M pyogenes aureus, E coli	8
A S	257187	29	F	Bilateral hydronephrosis	(250×4) ×6	B proteus, A aerogenes, S faecalis, E coli	B proteus, S faecalis	7
E C	822747	55	F	Bilateral hydronephrosis	(250×4) ×6	P aeruginosa, E coli	P aeruginosa, E coli	9
C A	195461	41	M	B P H , coronary	(250×4) ×5	A aerogenes, E coli, S faecalis	E coli	
I D	251365	30	M	Bilateral hydronephrosis	(500×4) ×7	M pyogenes aureus, diphtheroids	No growth	19
J K	258307	77	M	B P H , urinary retention	(250×4) ×6	M pyogenes aureus, A aerogenes	No growth	24
E D	045020	58	M	Bilateral renal calculi	(500×4) ×8	Para colon, P aeruginosa, S faecalis	A aerogenes	72
N F	256929	4 mo	F	Bladder neck stricture, bilateral hydronephrosis	(50×4) ×10	B pyocyaneus	P aeruginosa	6

TABLE 1 *Continued*

Name	Unit Number	Age	Sex	Diagnosis	Treatment	Culture Before Treatment	Culture After Treatment	Maximum Blood Level µg/ml
M S	174149	34	F	Neurogenic bladder	(500x4) x6	A aerogenes	A aerogenes	
T B	259373	56	M	B P H, staghorn calculus, rt	(500x4) x6	B proteus	B proteus, yeast cells	64
M D	227949	59	F	Ca bladder	(250x4) x6	E coli, A aerogenes, S faecalis	A aerogenes, S faecalis	0
T LeO	901682	45	F	Hematuria	(500x4) x6	A aerogenes, E coli	A aerogenes, E coli	38
P W	869645	61	F	Ca bladder	(500x4) x4	B proteus, S faecalis	No growth	12
P L	025237	8	M	Bilateral hydronephrosis	(250x4) x9	P aeruginosa	P aeruginosa	
P C	783557	68	M	Ca prostate	(500x4) x6	B proteus, A aerogenes	B proteus, A aerogenes	
H W	262617	65	M	B P H	(500x4) x6	No growth	E coli, A aerogenes	
W O'H	594212	78	M	B P H	(500x4) x6	B proteus, S faecalis	S faecalis, M pyogenes aureus, diphtheroids	
C A	936286	52	M	Ca bladder, extension to pelvis	(500x4) x10	Coliform, diphtheroids, E coli	Diphtheroids	
M M	442151	54	F	Urethral caruncle	(250)x4 x3	E coli, B proteus, S faecalis	S faecalis	
P S	152513	60	M	B P H, tabes, Charcot joint, prostatic calculus	(500x4) x10	B proteus, Strep faecalis	No report	
F M	831156		F	Post radiation cystitis, left renal calculus	(500x4) x5½	A aerogenes, S faecalis	A aerogenes, S viridans, diphtheroids	
G S	989307	65	M	Prostatic fibrosis	(500x4) x6	S faecalis, M pyogenes aureus	No growth	32
G S	254497	69	M	B P H	(500x4) x10	A aerogenes, S faecalis, E coli	A aerogenes, E coli	52
T M	855148	63	M	Left staghorn calculus	(500x4) x2	B proteus, S faecalis, M pyogenes aureus	B proteus, S faecalis, M pyogenes aureus	

TABLE 1 *Continued*

Name	Unit Number	Age	Sex	Diagnosis	Treatment	Culture Before Treatment	Culture After Treatment	Maximum Blood Level
								ug/ml
E I	034832	66	M	Chronic cystitis	(500x4)x7	E coli, S faecalis	E coli	
E S	719050	47	F	Pyuria	(500x4)x7	B proteus, M pyogenes aureus	No growth	
M A	216752	40	F	Pyuria, hematuria	(500x4)x7	M pyogenes aureus, diphtheroids	No growth	
E K	255276	65	M	B P.H , ca prostate, ?	(500x4)x7	B proteus, M pyogenes aureus, M tetragenes	B proteus	
B A	171978	59	F	Chronic cystitis, rectocele	(500x4)x7	M pyogenes, G tetragenes	M pyogenes, S faecalis	
M S	264681	44	F	Cystitis, urethral stricture	(500x4)x7	B proteus	No growth	
B B	226388	70	M	CNS lues, B P H with obstructive hiatus, hernia CVA	(500x4)x6	B proteus, S faecalis, S viridans	A aerogenes	
Y Y	267289	62	M	B P H , retention	(500x4)x7	No growth	No report	9
C P	260654	61	M	B P H	(500x4)x6	A aerogenes, S faecalis	E coli	
S Y	253766	59	M	Acute retention	(500x4)x6	S faecalis, B proteus	A aerogenes, diphtheroids	
G S	258506	16	F	Vaginourethral fistula, neurogenic bladder	(500x4)x6	A aerogenes, S faecalis	A aerogenes	45
C P	253373	72	M	B P H	(500x4)x6	A aerogenes, S faecalis, diphtheroids	A aerogenes, S faecalis	32
F H	250379	65	M	Renal calculus, bilateral, bladder neck contracture	(500x4)x2	A aerogenes, E coli, S faecalis	E coli, A aerogenes	
C C	924445	25	F	Pyelonephritis, cystitis	(500x4)x6		No growth	64
L S	221040	62	M	Hematuria	(500x4)x6	E coli, diphtheroids, S faecalis	E coli	

TABLE 1 *Continued*

Name	Unit Number	Age	Sex	Diagnosis	Treatment	Culture Before Treatment	Culture After Treatment	Maximum Blood Level
								ug/ml
F L	003536	75	M	B P H	(500×4) ×2	S faecalis	No growth	18
Y M	257767	61	M	B P H	(500×4) ×7	M pyogenes aureus, diphtheroids	No growth	40
G K	701982	68	M	B P H , diabetes	(500×4) ×7	B proteus, S faecalis	No growth	
C	936657	54	F	Papilloma of bladder	(250×4) ×1	M pyogenes aureus, S faecalis	Enterococci	
L R	705708	70	F	Kidney stones (bilateral)	(500×4) ×7	E coli		
H N	263392	70	M	B P H , urethral stricture	(500×4) ×6	E coli	No growth	
F F	053590	60	F	Chronic cystitis	(250×4) ×9	E coli, S faecalis	Diphtheroids	

TABLE 2 *Effect of novobiocin treatment on urinary cultures in 60 patients with urinary infections*

<table>
<tr><th></th><th><i>A aerogenes</i></th><th><i>E coli</i></th><th><i>B proteus</i></th><th><i>P aeruginosa</i></th><th><i>S faecalis</i></th><th><i>S viridans</i></th></tr>
<tr><td>Positive before treatment</td><td>18</td><td>15</td><td>21</td><td>6</td><td>29</td><td>2</td></tr>
<tr><td>Positive after treatment</td><td>13</td><td>13</td><td>10</td><td>5</td><td>13</td><td>2</td></tr>
<tr><td></td><td colspan="2"><i>M pyogenes aureus</i></td><td colspan="2"><i>G tetragenes</i></td><td colspan="2"><i>Diphtheroids</i></td></tr>
<tr><td>Positive before treatment</td><td colspan="2">15</td><td colspan="2">6</td><td colspan="2">7</td></tr>
<tr><td>Positive after treatment</td><td colspan="2">4</td><td colspan="2">3</td><td colspan="2">6</td></tr>
</table>

* Eight other patients whose urine cultures were negative for A aerogenes before treatment became positive following medication

of novobiocin resistant bacteria In case novobiocin sensitive bacteria reappear at a later date, then such patients can not be considered improved Accordingly, there were 11 patients who were 'cured' because their urine cultures showed no growth Eleven of 21 cases of B proteus, 16 of 29 cases of S faecalis, 11 cases of 15 M pyogenes aureus, 2 cases of 15 E coli, 3 cases of 6 G tetragenes and one case each of 6 P aeruginosa and 7 diphtheroids were 'improved' in that the organisms which were sensitive to novobiocin were eradicated

Figure 1 shows in graphic form the serum levels in 16 patients who were given 500 mg of novobiocin four times daily Two patients were given 250 mg four times daily The average levels range between 20–50 ug/ml In one case, a serum level of 120 ug/ml was recorded on the fifth day These levels are more than

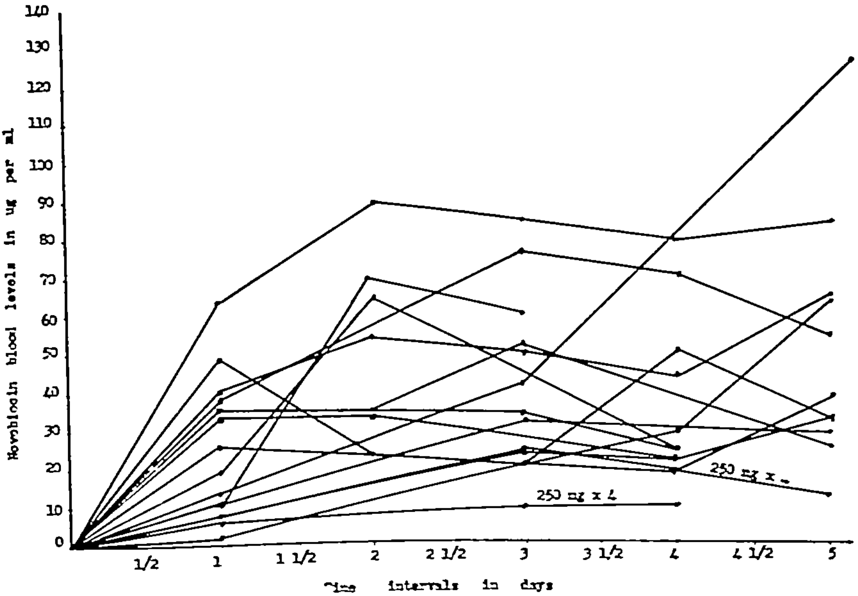

FIG 1 Novobiocin blood serum levels in ug/ml following oral administration of 500 mg four times daily except in two cases where 250 mg four times daily was administered

adequate to control or inhibit pathogenic bacteria which are sensitive to novobiocin in range of 0 1 to 10 ug/ml Two hundred fifty mg four times daily gave a minimum level of 6 ug ml and a maximum of 23 ug/ml These levels may not be therapeutically satisfactory in cases where the pathogens are even slightly resistant to novobiocin These findings indicate that novobiocin is very well absorbed from the intestinal tract, and that parenteral administration may not be necessary, except when the gastrointestinal tract of the patient can not tolerate the drug No other antibiotic of therapeutic value gives such high blood levels We were unable to explain the reason why no novobiocin levels could be detected in two patients Perhaps these patients did not take the drug, or absorption from the gastrointestinal tract was not satisfactory

TOLERANCE

In general the patients tolerated novobiocin well In two cases the drug had to be discontinued because of vomiting or epigastric pain One patient had a maculopapular skin rash and the diagnosis was dermatitis medicamentosa The rash appeared on the first day the drug was administered It was pruritic and involved the back and upper and lower extremities including the wrists and palms The drug was continued until the patient had had six days of novobiocin therapy Bland dermatological lotions were applied and the rash faded away Two patients had nausea, one each had vomiting, ringing in the ears and epigastric pains

No changes in the white or red cell counts or hemoglobin levels were observed during the course of the treatment of these 60 patients on this dosage No toxic

TABLE 1 *Continued*

Name	Unit Number	Age	Sex	Diagnosis	Treatment	Culture Before Treatment	Culture After Treatment	Maximum Blood Level
								ug/ml
F L	003536	75	M	B P H	(500×4) ×2	S faecalis	No growth	18
Y M	257767	61	M	B P H	(500×4) ×7	M pyogenes aureus, diphtheroids	No growth	40
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L R	705708	70	F	Kidney stones (bilateral)	(500×4) ×7	E coli		
H N	263392	70	M	B P H, urethral stricture	(500×4) ×6	E coli	No growth	
F F	053590	60	F	Chronic cystitis	(250×4) ×9	E coli, S faecalis	Diphtheroids	

TABLE 2 *Effect of novobiocin treatment on urinary cultures in 60 patients with urinary infections*

	A aerogenes	*E coli*	*B proteus*	*P aeruginosa*	*S faecalis*	*S viridans*
Positive before treatment	18	15	21	6	29	2
Positive after treatment	13	13	10	5	13	2
	M pyogenes aureus		*G tetragenes*		*Diphtheroids*	
Positive before treatment	15		6		7	
Positive after treatment	4		3		6	

* Eight other patients whose urine cultures were negative for A aerogenes before treatment became positive following medication

of novobiocin resistant bacteria In case novobiocin sensitive bacteria reappear at a later date, then such patients can not be considered improved Accordingly, there were 11 patients who were 'cured' because their urine cultures showed no growth Eleven of 21 cases of B proteus, 16 of 29 cases of S faecalis, 11 cases of 15 M pyogenes aureus, 2 cases of 15 E coli, 3 cases of 6 G tetragenes and one case each of 6 P aeruginosa and 7 diphtheroids were 'improved' in that the organisms which were sensitive to novobiocin were eradicated

Figure 1 shows in graphic form the serum levels in 16 patients who were given 500 mg of novobiocin four times daily Two patients were given 250 mg four times daily The average levels range between 20–50 ug/ml In one case, a serum level of 120 ug/ml was recorded on the fifth day These levels are more than be observed with single drugs It is therefore important to bear in mind that it is only a question of time before Micrococcus aureus will develop resistance to novobiocin Unpublished reports from our laboratories indicate that Proteus and Pseudomonas gradually develop increased resistance to tetracycline so that they survive in a concentration of 3 500 ug/ml tetracycline[11] It is therefore feasible to anticipate more failures to novobiocin therapy in Proteus infections as the drug is used more extensively Studies are in progress to determine the genetic nature of S faecalis in relation to mutation or increased resistance to this and other antibiotics

SUMMARY

Sixty patients suffering from various urological conditions, with infections caused by a variety of pathogenic bacteria were treated with novobiocin with the following results

It cleared the urine of 11 out of 15 M pyogenes aureus infections, 16 out of 29 S faecalis 11 out of 21 B proteus 3 out of 6 G tetragenes, 2 out of 15 E coli, one out of 7 diphtheroids and 6 P aeruginosa

However, 73 per cent of infections with M pyogenes aureus (Staphylococcus) were eradicated as were 55 per cent of S faecalis infections, 52 per cent of Proteus infections and 50 per cent of Gaffkya tetragenes infections

Thirteen per cent of E coli infections, 14 per cent of diphtheroid and 17 per cent of Pseudomonas infections were also eradicated

It cleared 5 of 18 cases of A aerogenes, but 8 patients who did not have A aerogenes before treatment had positive cultures for this organism later, despite the medication It also failed to cure 2 S viridans infections

In only 11 out of 60 patients were the urine cultures completely sterilized by treatment with novobiocin

Five hundred mg of novobiocin four times daily resulted in satisfactory serum levels averaging 20 to 50 ug ml

One patient experienced mild dermatitis medicamentosa two patients had to discontinue medication because of vomiting or epigastric pain, but all the remaining cases tolerated the drug very well.

When novobiocin was tested in vitro, drug resistance appeared to increase rapidly, suggesting that this drug may best be used in combination with other drugs such as tetracycline rather than alone

Novobiocin was effective against many infections with B proteus, Micrococcus aureus and S faecalis It was also effective against some infections with E coli and P aeruginosa

This study was aided in part by a grant from Merck Sharpe and Dohme Research Laboratories which also graciously provided the novobiocin used, as well as much technical assistance Their help is gratefully acknowledged

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[11] Seneca H Lattimer J K and Troc O K The limit of maximum bacterial resistance to antibiotics In press

effects on renal function were observed, and elevated blood urea nitrogen was not affected adversely by novobiocin Welch and associates[6] reported that of 208 subjects given 10 gm novobiocin orally over a 12 day period, only one had a rash, 3 showed yellow discoloration of the sclerae which faded gradually on the discontinuation of the drug On the other hand, Cook and associates[7] reported skin rashes in 6 of 23 patients treated with novobiocin

DISCUSSION

Trafton and Lind[8] reported on novobiocin in the treatment of genitourinary infections Two of seven cases of S faecalis were cured and five improved, three of nine cases of M pyogenes aureus infections were cured, four were improved and two failed to respond, one of five cases of Proteus infections was cured, 3 were improved and one failed, in two cases each of A aerogenes and E coli infections no effect was observed They concluded that in urinary tract infections involving M pyogenes aureus, S faecalis and certain strains of Proteus that were resistant to penicillin and other antibiotics, novobiocin was clinically effective Their patients had blood levels of 6 25 to 87 ug/ml Cook and associates[7] treated 20 patients with acute pneumococcal and staphylococcal infections with novobiocin In 9 cases, it was the only drug used The response to therapy was *eminently satisfactory, in only one case did novobiocin fail to alter the* course of the infection In three other cases, its efficacy could not be judged In the series reported here, novobiocin treatment eliminated 2 of 15 E coli infections, 11 of 21 Proteus infections, 16 of 29 S faecalis infections, 11 of 15 M pyogenes aureus infections, 3 of 6 G tetragenes infections, one of 7 diphtheroid and 1 of 6 Pseudomonas infections, 5 of 18 A aerogenes infections, but 8 other cases acquired A aerogenes infections despite novobiocin treatment Two cases of S viridans infections failed to respond to treatment

The genetic constitution of M pyogenes aureus is such that it develops resistance to antibiotics in due time In our laboratories, we[9] have evolved micrococci which are resistant to 50,000 units/ml penicillin Similarly, micrococci are showing increased resistance to tetracycline, chloramphenicol, bacitracin and erythromycin-carbomycin-novobiocin-oleandomycin series Jawetz and associates[10] reported that a single exposure of *10^6 staphylococcus/ml* to subinhibitory concentration of novobiocin resulted in emergence of variants 10 to 30 fold more resistant than the original strain For this reason, novobiocin should not be used alone in the treatment of staphylococcal infections Combination with other antibiotics resulted in striking bactericidal effects, far in excess of

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[6] Welch, H , Lewis, C N , Putman, L E and Randall, W A *A study of the sensitizing potential of novobiocin* Ant Med Clin Ther , 3 27, 1956

[7] Cook, E , Eastmann, G and Bunn, P Use of novobiocin in the management of acute pneumococcal and staphylococcal infections Antibiotic Annual, 1957, p 396 New York Medical Encyclopedia

[8] Trafton, H M and Lind, H E Novobiocin in the treatment of urinary tract infections Antibiotic Annual, 1957, p 420 New York Medical Encyclopedia

[9] Seneca, H , Lattimer, J K and Troc, O K Some implications of increasing antibiotic resistance of Micrococcus A M A Arch Path , 64 481, 1957

[10] Jawetz, E , Bertie, W and Sonne, M Participation of novobiocin and vancomycin in combined antibiotic action against staphylococci Ant Med Clin Ther , 4 40, 1957

TABLE 1 *Total discharges from the sanatorium over a 10-year period with the number of cases of genitourinary tuberculosis and the number of cases of symptomless bacilluria*

Year	Total Discharges from Sanatorium	Total Cases of Genito-Urinary Tuberculosis	Cases of Symptomless Bacilluria
1956	736	46	4
1955	746	53	5
1954	627	49	6
1953	557	37	5
1952	495	49	5
1951	540	25	1
1950	509	29	0
1949	505	27	4
1948	426	26	3
1947	422	35	3
Total 10 yrs	5563	376	36

TABLE 2 *Pyelographic findings*

Pyelographic findings	No of Cases
No demonstrable disease	18
Minimal disease	3
Moderate disease	1
Severe disease	4
Not done (too ill etc)	10

Associated tuberculosis Every case had active tuberculosis of some organ as all were in sanatorium under treatment Thirty-two had active tuberculosis of lungs or pleura, 17 had orthopedic tuberculosis and four had miliary tuberculosis

Status of admission urine in centrifuged voided specimen Out of the 36 cases, 21 had no pus cells or only an occasional pus cell in the urine, 10 had 2–4 pus cells and 5 had 5–9 pus cells reported No cases in this series had any red cells

Time of diagnosis Twenty-one cases were diagnosed on the admission urine cultures Of the 15 cases diagnosed later, 13 were orthopedic cases and were discovered through the regular quarterly urine cultures for tubercle bacilli

Pyelographic findings (table 2) In the four cases with severe pyelographic changes, one case had no white blood cells in the urine two cases 2–4 white blood cells, and the fourth case 4–9 white blood cells

Site of lesion In 21 of the 36 cases it was possible to demonstrate the site of the lesion by intravenous or retrograde pyelograms by ureteral cultures or at autopsy In 13 cases apparently only one kidney was involved In 5 cases both kidneys were involved, and in 3 cases apparently only the prostate gland, seminal vesicles or epididymides The lesions in this last group came to light subsequent to the finding of a positive urine culture Five cases were too ill to warrant investigation and did not come to autopsy The remaining 10 cases were investigated but the source of the positive urine cultures was not demonstrated

Autopsies (table 3) In seven out of nine known deaths it was possible to check

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SYMPTOMLESS TUBERCULOUS BACILLURIA

GODFREY L GALE

From the Toronto Hospital for Tuberculosis, Weston, Ontario, Canada

This study was undertaken to try to discover the incidence of unsuspected genitourinary tuberculosis among routine admissions to the Toronto Hospital for Tuberculosis, Weston, Ontario For many years every admission to this sanatorium has had a urine specimen cultured for tubercle bacilli In addition all patients with bone and joint tuberculosis have had the urine culture repeated quarterly throughout their stay in the sanatorium This latter measure was instigated by Dr R I Harris following his classical research in 1929[1] showing the frequent association of renal tuberculosis with bone and joint tuberculosis, due to the fact that these cases had a bloodstream infection with tubercle bacilli The staff of the sanatorium believes that a small but definite number of cases of unsuspected genitourinary tuberculosis were discovered in this way, but more accurate information was required

Therefore a survey was made of all the cases of genitourinary tuberculosis discharged from the sanatorium over the 10-year period 1947–1956 (table 1) It will be seen that cases of genitourinary tuberculosis form 6 8 per cent of the total discharges and that 9 8 per cent of the cases of genitourinary tuberculosis were symptomless and unsuspected at the time of admission

TERMS OF REFERENCE

The term, symptomless tuberculous bacilluria was used under the following conditions

1) No past history of genitourinary disease of any kind which would direct the observer's attention to these viscera

2) No urinary symptoms of any kind

3) No abnormal physical signs in the genitourinary tract such as a "boggy" prostate gland, nodules in the epididymis or tenderness in the flank

4) No red cells at all in the urine

5) Less than 10 pus cells in the centrifuged specimen of *voided* urine In actual fact nearly two-thirds of the cases had clear urine with no pus cells or only an occasional pus cell reported

Two further points need clarification These cases do not include gynecological tuberculosis, and the diagnosis of genitourinary tuberculosis was made on the presence of positive urine cultures The finding of acid fast bacilli in the urine does not constitute a diagnosis of tuberculosis

ANALYSIS

Age and sex The age varied from 3 to 76 years, with 7 cases under 16 and the largest section in the 16 to 30 year group There were 22 males and 14 females

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Read at annual meeting of Canadian Tuberculosis Association, Vancouver, B C June 24–28, 1957

[1] Harris, R I Tuberculous bacilluria Brit J Surg, **16** 464, 1929

cavitation in the kidneys but are symptomless and at times show tubercle bacilli in the urine without appreciable numbers of pus cells

Is it possible to excrete tubercle bacilli in the urine without a definite tuberculous focus? We accept the conclusions of Medlar[2, 3] Band[4] and many other investigators that the presence of tubercle bacilli in the urine indicates a definite lesion in the genitourinary tract

It is believed that a culture of the urine for tubercle bacilli on all admissions and a quarterly urine culture on all cases of tuberculosis of the bones and joints are simply procedures that will bring to light cases of genitourinary tuberculosis which might otherwise be overlooked

SUMMARY

Over the 10-year period of 1947–1956, 36 cases of unsuspected genitourinary tuberculosis have been discovered through culture of the urine of 5563 sanatorium admissions and the quarterly culture of the urine of the 814 cases of bone and joint tuberculosis

These patients had no previous history of genitourinary disease, no abnormal physical signs or symptoms and no red cells in the urine All had less than 10 pus cells in the centrifuged, voided urine and most had no pus cells at all or only an occasional pus cell

Most of these cases had early and minimal renal lesions but a proportion had moderately advanced or advanced renal tuberculosis

Renal tuberculosis can at times be a silent and insidious disease

The author wishes to express his appreciation to Dr C A Wicks, superintendent, Toronto Hospital for Tuberculosis, Weston, Ontario, and to Dr J C McClelland and Dr W K Kerr, consultants in urology, for much helpful advice Many of the foregoing cases were under the care of the late Dr K F Davis

Medlar G M The significance of tubercle bacilli in the urine Urol and Cutan Rev 36 71, 1932

[3] Ordway, W H and Medlar, E M Tuberculous bacilluria A ten-year study J A M A, 119 937, 1942

[4] Band D Renal tuberculosis Histopathology and pathogenesis Edinburgh M J, 42 162 1935

TABLE 3 *Autopsy findings correlated with urine findings on admission and shortly before death*

No	Pathological Findings in Kidneys	Admission Urine	Final Urine Before Death	Time Interval
1	Massive caseous necrosis	*clear*	*18–20 w b c*	*12 mos*
2	Caseous tuberculosis	clear	30–35 w b c	17 mos
3	Extensive caseation	2–4 w b c	25–30 w b c	10 mos
4	Multiple early caseous lesions	2–4 w b c	2–3 w b c	14 dys
5	A small lesion in one pyramid	clear	2–3 w b c	3 yrs
6	Kidneys healthy Tuberculosis in prostate, sem ves & epidid	2–4 w b c	Many w b c & r b c	26 mos
7	No tuberculosis in kidneys in routine autopsy (female)	2–4 w b c	5–6 w b c	4 yrs

TABLE 4 *Status 6 months to 10 years*

Status	No of Cases
Well and working	14
Well, not yet working	3
Under treatment	1
Dead, from tuberculosis	7
Dead, not from tuberculosis	2
Unknown	9

the findings in the urine by autopsy Most of these cases occurred in the early days of drug therapy

Effect of treatment on urine cultures Twenty-five cases became and remained negative for tubercle bacilli in the urine Eight cases continued to have positive cultures to time of death or discharge, and in three cases data were insufficient to estimate the effect of treatment Three cases had nephrectomy and 13 had adequate courses of chemotherapy by modern standards

Followup (table 4) No detailed followup was attempted in these cases However, the tabulation shows the status of these patients, when last contacted, with a followup of 6 months to 10 years

DISCUSSION

This small study indicates that a certain number of routine admissions to sanatoria have unsuspected genitourinary tuberculosis This can be diagnosed at the time of admission by culturing the urine for tubercle bacilli before drug treatment is started In most cases the renal lesion if present will be small and perhaps hard to demonstrate at this stage in pyelograms, but a proportion will have moderately or even far advanced renal tuberculosis Yet their lesion is at times apparently quite silent This has been borne out recently in another study made at this sanatorium to be published shortly in which a series of proven cases of renal tuberculosis has been followed for over 20 years This demonstrated the fact that a surprising number of cases of renal tuberculosis can become "good chronics" like some cases of pulmonary tuberculosis Such cases have persisting

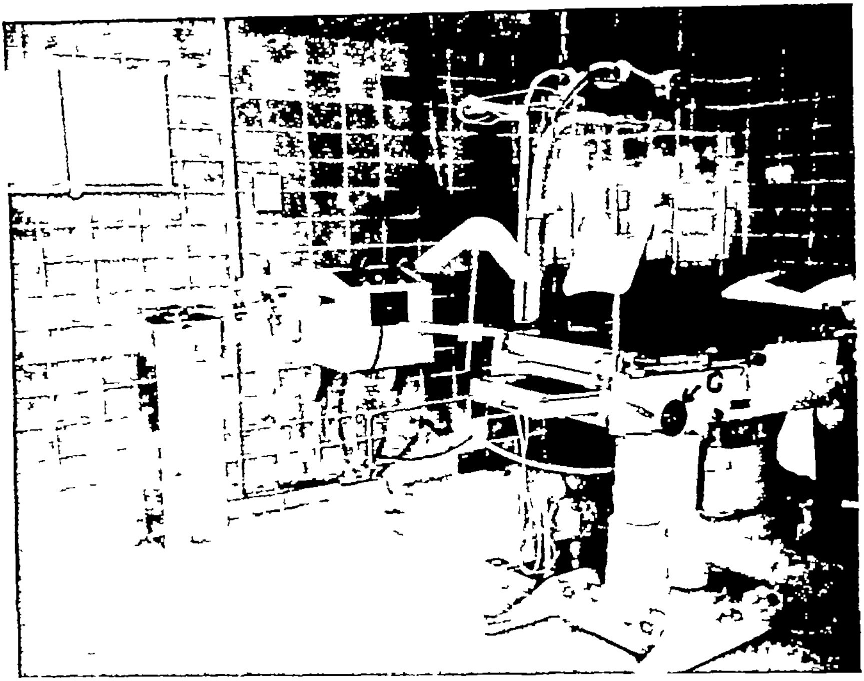

FIG 1 *Over-all view of apparatus installed with cystoscopy table*

Pressure remote control instrument is mounted on cystoscopy table Knob (C) regulates pressure Diaphragm type water pressure regulator, fluid flow directing valves, manometer, and glycine tank are mounted on wall adjacent table

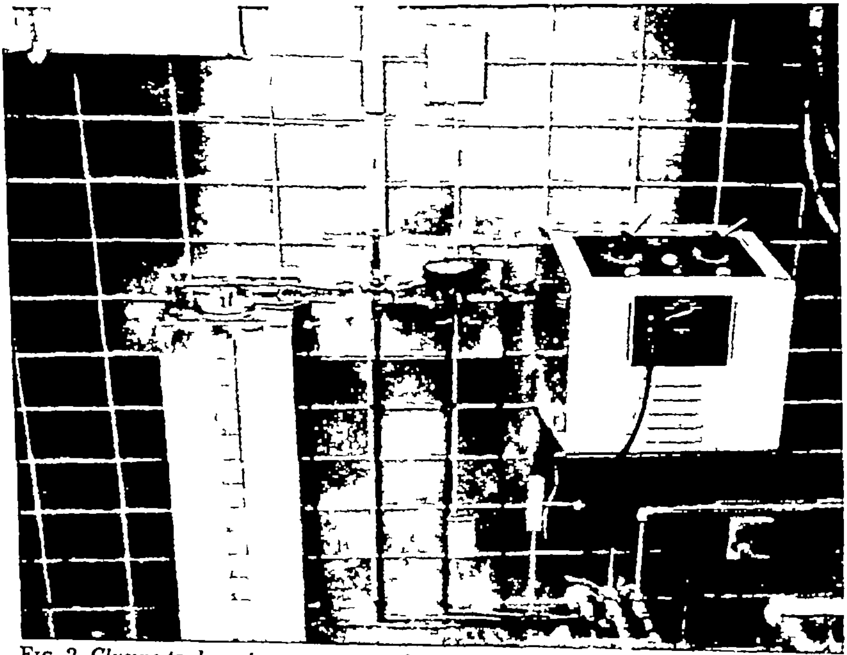

FIG 2 *Glycine tank, water pressure regulator, manometer and control valves wall mounted adjacent cystoscopy table*

For explanation see schematic drawings figures 3 to 6

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FLUID SUPPLY APPARATUS FOR CYSTOSCOPY AND TRANSURETHRAL OPERATIONS

FREDERIC E B FOLEY

From the Urologic Department of the Charles T Miller Hospital, St Paul, Minn

Cystoscopy and transurethral operations require a supply of irrigating fluid to the cystoscope, resectoscope, or other transurethral operating instrument

Pressure under which the fluid is supplied and the rate of its flow into the bladder should be alterable and adjusted to changing conditions of the operative procedure

The long employed means for altering pressure and its resultant flow rate of fluid to the bladder has been the adjustable height percolator raised and lowered by rope over ceiling pulleys or other mechanism This means is absolutely accurate, foolproof and functions perfectly The value and importance of this simple device to the practice of urology are rarely contemplated or appreciated But the adjustable height percolator, despite its importance and usefulness, is inconvenient, troublesome and cumbersome Each alteration of pressure and flow rate requires raising or lowering the percolator by its inconvenient mechanism Repeatedly the percolator must be manually replenished with fluid carried to it Usually the operative procedure must be interrupted while the percolator is lowered, refilled and re-elevated Resterilization of the percolator and its rubber tubing supply line to the instrument is troublesome and elaborate

Numerous attempts[1] [3] have been made to eliminate some of the various undesirable and inconvenient features of the percolator These attempts have not been completely successful

The above ceiling sterile water tank with gravity feed supply line to the bladder, as present in most new cystoscopy room installations, at first sight promised to provide the required functions and eliminate the inconvenient and troublesome percolator

But the above ceiling tank was soon found to be not the blessing it promised

1) Its 7 to 9 foot height above the bladder gives an undesirably high and dangerous pressure capable even of rupturing the bladder and capable also of rapid extravasation of water, which is hypotonic and injurious, into open tissue spaces and bloodstream

2) In response to the unduly high pressure, the rate of flow is much greater than needed except in presence of brisk bleeding when a very rapid flow may be required to permit vision At other times the superfluous rapidity of flow requires frequent interruptions of the procedure to empty the quickly filled-to-capacity bladder

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Read at annual meeting of North Central Section of American Urological Association, Mackinac Island, Mich , August 29-31, 1957

[1] Creevy, C D Personal communication

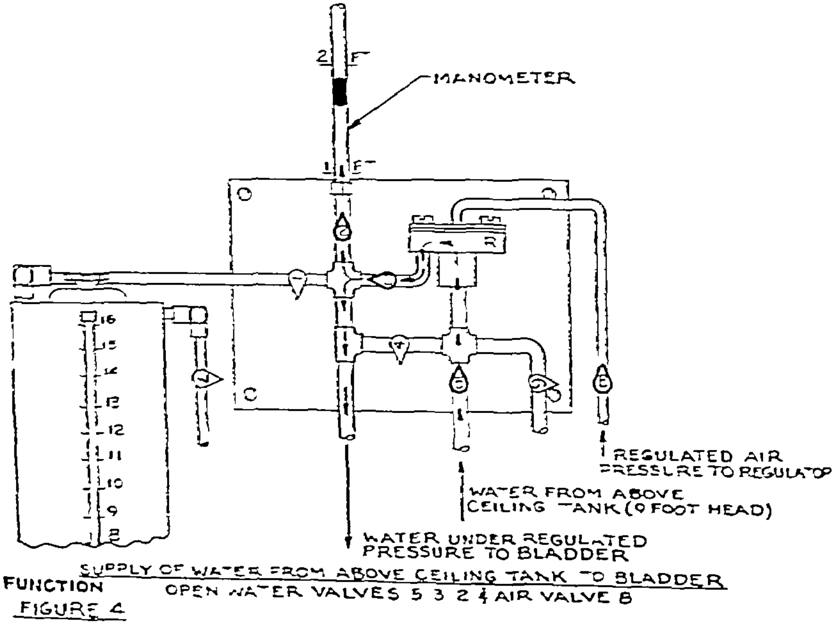
[2] Doss, A K Personal communication (American Cystoscope Makers Inc catalogue No 2935)

[3] Foley, F E B Urologist Correspondence Club Letters, vol 20, July 18, 1955

Diaphragm type commercially made water pressure regulators are extensively used For example they are used with drinking fountains to reduce the initial city water supply pressure of 60 p.s.i. which is 140 feet, down to 2 p.s.i. which is 5 feet Such regulators function by means of screw adjustment of the pressure of a spring applied to the top surface of a small area stiff diaphragm.

Exhaustive inquiry failed to find a commercially made water pressure regulator of this sort capable of operating at the very low pressures required for this application which are initial pressure 9 feet and adjustable range of reduced pressure from 7 feet down to 1 foot

For want of an available commercially made water pressure regulator of this sort, I designed and made a very sensitive and accurate diaphram type regulator which functions perfectly at these very low pressures This was accomplished by use of a proportionately very large area, very pliable diaphragm and replacing spring pressure on its top surface by very accurately regulated air pressure The latter is provided by an amazingly sensitive and accurate air pressure regulator manufactured by Minneapolis Honeywell Heat Regulator Company This instrument will reduce an initial air supply pressure to any desired value accurately to within one four-thousandth of a pound per square inch which is equivalent to one eighth of an inch of water height


2 F
MANOMETER
1 F
C
R
16
15
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10
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8
REGULATED AIR PRESSURE TO REGULATOR
WATER FROM ABOVE CEILING TANK (9 FOOT HEAD)
WATER UNDER REGULATED PRESSURE TO BLADDER
SUPPLY OF WATER FROM ABOVE CEILING TANK TO BLADDER
FUNCTION
OPEN WATER VALVES 5 3 2 & AIR VALVE 8
FIGURE 4

Fig 4 *Supply of water from above ceiling tank to bladder under regulated pressure*

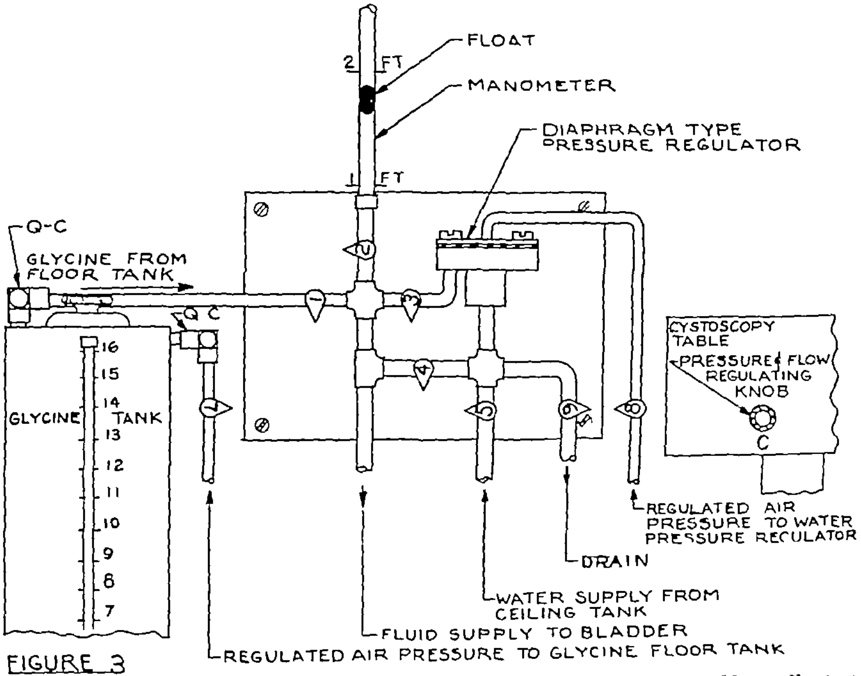
For this function valves (2), (3), (5) and (8) are opened Water from above ceiling tank via valve (5) under pressure of 9 foot head is delivered to pressure regulator (R) Accurately regulated air pressure via valve (8) (adjusted by the knob C figures 1 and 3) applied to the diaphragm of water pressure regulator reduces initial 9 foot pressure to any desired value Fluid passing from regulator through valve (3) is supplied to bladder under desired reduced pressure Manometer accurately indicates this pressure

3) *Flow rate can be reduced only by* valve adjustment restriction of the supply line which does not remove the danger of high pressure if supply of water is inadvertently continued beyond safe bladder distention

4) There is no means of adding glucose, glycine or other non-electrolytic substance to the ceiling tank for making an isotonic fluid A non-electrolytic irrigating fluid is required during use of the high frequency current for fulguration and cutting

During the past two years I have made continuous effort and experiment to devise an irrigating apparatus combining the virtues of the adjustable height percolator with those of the above ceiling tank, at the same time eliminating the objectionable features of both This purpose has been accomplished in the apparatus here described

The apparatus permits supply of sterile water from the above ceiling tank by *gravity feed under regulated pressure and flow rate the exact equivalent of the* adjustable height percolator This is accomplished by means of a diaphragm type reducing valve or water pressure regulator so sensitive and accurate that the pressure may be regulated in fractions of an inch of water height to any value between the full head of 9 feet and zero



FLOAT
2 FT
MANOMETER
DIAPHRAGM TYPE PRESSURE REGULATOR
1 FT
Q-C
GLYCINE FROM FLOOR TANK
Q C
1
2
3
4
5
6
7
8
16
15
14
13
12
11
10
9
8
7
GLYCINE TANK
CYSTOSCOPY TABLE
PRESSURE & FLOW REGULATING KNOB
C
REGULATED AIR PRESSURE TO WATER PRESSURE REGULATOR
DRAIN
WATER SUPPLY FROM CEILING TANK
FLUID SUPPLY TO BLADDER
REGULATED AIR PRESSURE TO GLYCINE FLOOR TANK
FIGURE 3

Fig 3 *Schematic drawings showing apparatus installed with cystoscopy table as illustrated in figures 1 and 2*

All fluid directing valves 1 to 6 and air directing valves 7 and 8 are shown in closed position When valve number is horizontal (4) valve is closed, when upright (4) valve is open Remote pressure and flow control instrument (C) is mounted on cystoscopy table where it may be operated by surgeon or assistant It is an extremely sensitive and accurate air pressure regulator It is supplied with initial air pressure of 20 p s i from air line of room temperature thermostat present in most hospital rooms Functions of apparatus, provided by opening the required valves, are shown in figures 4 to 6

With this combination of sensitive water pressure regulator and hypersensitive air pressure regulator the initial 9 foot head of water pressure from the above ceiling tank may be regulated to within less than one inch of any desired pressure from 9 feet to zero Function of the apparatus is the exact equivalent of the adjustable height percolator

The apparatus also provides for supply of isotonic fluid under similarly regulated pressure and flow the exact equivalent of the percolator The isotonic fluid is supplied to the bladder from a 16 gallon capacity tank at floor level The fluid is displaced from tank to bladder by accurately regulated air pressure applied to the tank

The supply lines to the bladder from the water pressure regulator and floor level glycine tank connect with a wall manometer containing a conspicuous colored float atop the fluid column easily read from considerable distance Level of this float is the exact equivalent of percolator height

The hypersensitive air pressure regulator with its knob which regulates pressure and flow is mounted on the cystoscopy table where it may be operated by the surgeon or an assistant Setting the fluid directing valves 1 to 6 and air directing valves 7 and 8 (figs 3 to 6) produce the desired functions of the apparatus

The photographs and schematic drawings (figs 1 to 6) show the apparatus as installed at the Miller Hospital mounted on the wall along side the table and illustrate its functions

The apparatus described has been in use at the Miller Hospital and functions well It is hoped it may be made commercially available for those who may wish to employ it

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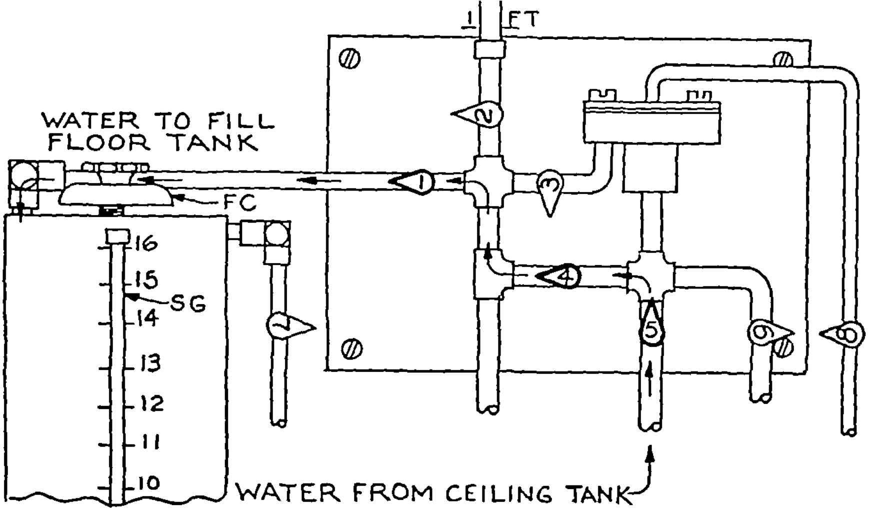


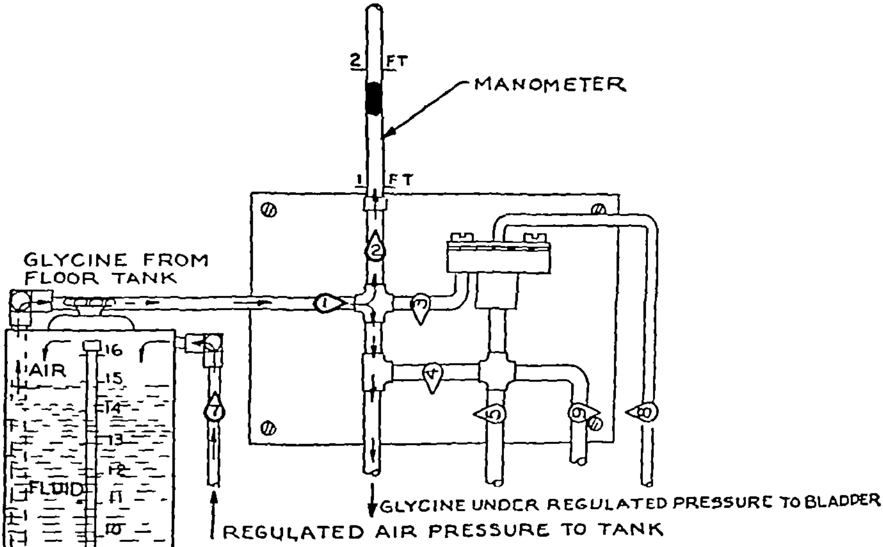
FUNCTION WATER FROM CEILING TANK TO FILL FLOOR TANK FOR MAKING GLYCINE MIXTURE

OPEN FLUID VALVES 5, 4, 1

FIGURE 5

Fig 5 *Supply of water from ceiling tank to floor tank for making glycine mixture*

For this function valves (5), (4) and (1) are opened Water from above ceiling tank under gravity feed passes to glycine tank via valves (5), (4) and (1) Graduations on glycine tank sight glass (S G) indicate volume of water in tank Required volume of glycine concentrate is added through tank top opening later sealed by filler cap (F C)


2 FT
MANOMETER
1 FT
GLYCINE FROM FLOOR TANK
AIR
FLUID
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GLYCINE UNDER REGULATED PRESSURE TO BLADDER
REGULATED AIR PRESSURE TO TANK

FUNCTION SUPPLY OF GLYCINE FROM FLOOR TANK TO BLADDER

OPEN FLUID VALVES 1, 2 & AIR VALVE 7

FIGURE 6

Fig 6 *Supply of glycine fluid from floor tank to bladder under regulated pressure*

For this function valves (1), (2) and (7) are opened Accurately regulated air pressure via valve (7) adjusted by knob C (figs 1 and 3) is applied to glycine tank Glycine fluid is displaced from tank via valve (1) to bladder and to manometer via valve (2) Pressure under which glycine fluid is supplied to bladder is indicated by manometer

With this combination of sensitive water pressure regulator and hypersensitive air pressure regulator the initial 9 foot head of water pressure from the above ceiling tank may be regulated to within less than one inch of any desired pressure from 9 feet to zero Function of the apparatus is the exact equivalent of the adjustable height percolator

The apparatus also provides for supply of isotonic fluid under similarly regulated pressure and flow the exact equivalent of the percolator The isotonic fluid is supplied to the bladder from a 16 gallon capacity tank at floor level The fluid is displaced from tank to bladder by accurately regulated air pressure applied to the tank

The supply lines to the bladder from the water pressure regulator and floor level glycine tank connect with a wall manometer containing a conspicuous colored float atop the fluid column easily read from considerable distance Level of this float is the exact equivalent of percolator height

The hypersensitive air pressure regulator with its knob which regulates pressure and flow is mounted on the cystoscopy table where it may be operated by the surgeon or an assistant Setting the fluid directing valves 1 to 6 and air directing valves 7 and 8 (figs 3 to 6) produce the desired functions of the apparatus

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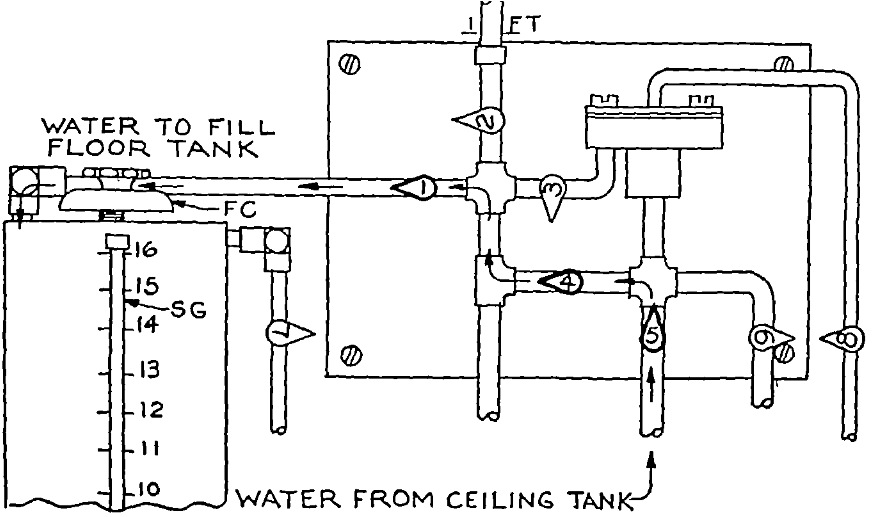

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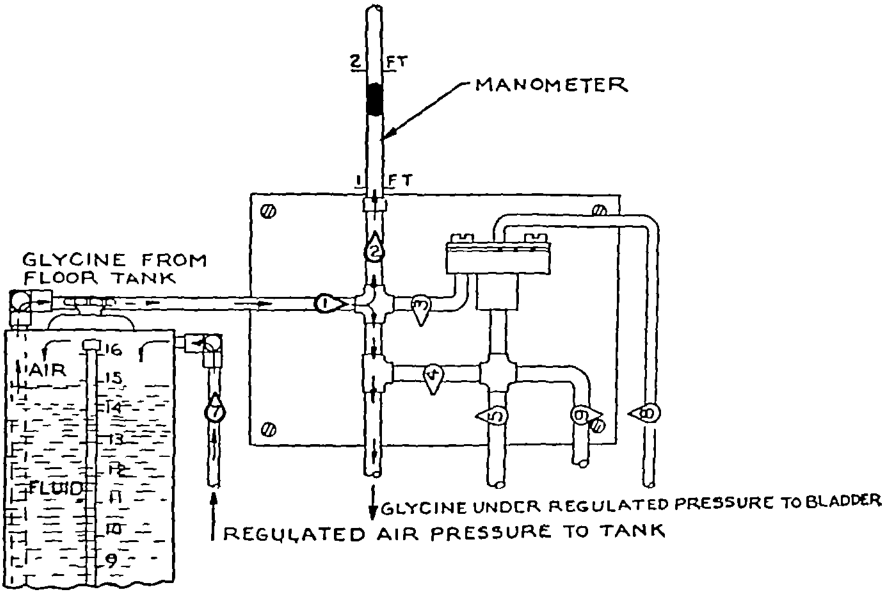
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GLYCINE UNDER REGULATED PRESSURE TO BLADDER
REGULATED AIR PRESSURE TO TANK

FUNCTION SUPPLY OF GLYCINE FROM FLOOR TANK TO BLADDER

OPEN FLUID VALVES 1, 2 & AIR VALVE 7

FIGURE 6

FIG 6 *Supply of glycine fluid from floor tank to bladder under regulated pressure*

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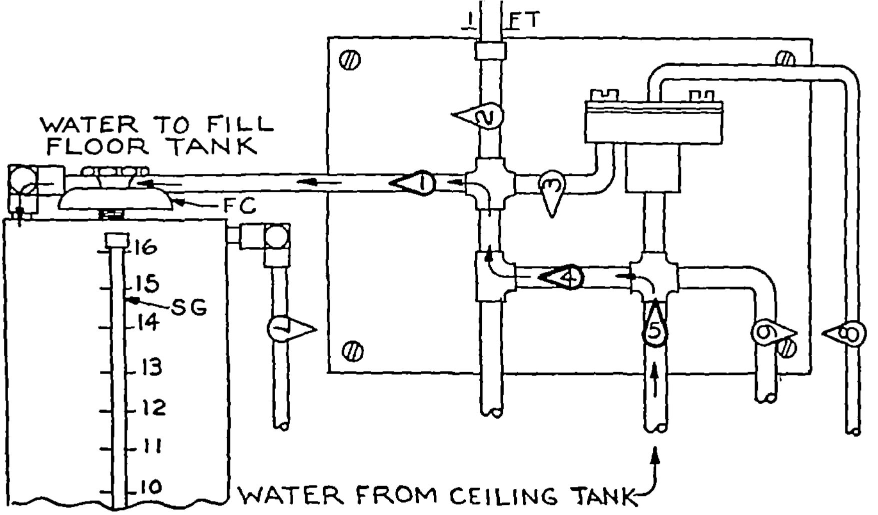

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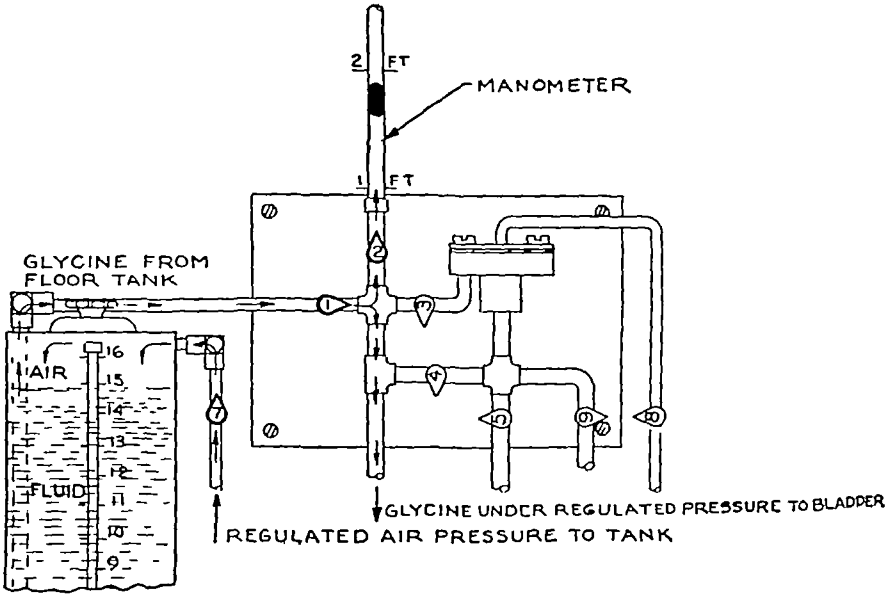
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8
GLYCINE UNDER REGULATED PRESSURE TO BLADDER
REGULATED AIR PRESSURE TO TANK

FUNCTION SUPPLY OF GLYCINE FROM FLOOR TANK TO BLADDER

OPEN FLUID VALVES 1, 2 & AIR VALVE 7

FIGURE 6

Fig 6 *Supply of glycine fluid from floor tank to bladder under regulated pressure*

For this function valves (1), (2) and (7) are opened Accurately regulated air pressure via valve (7) adjusted by knob C (figs 1 and 3) is applied to glycine tank Glycine fluid is displaced from tank via valve (1) to bladder and to manometer via valve (2) Pressure under which glycine fluid is supplied to bladder is indicated by manometer

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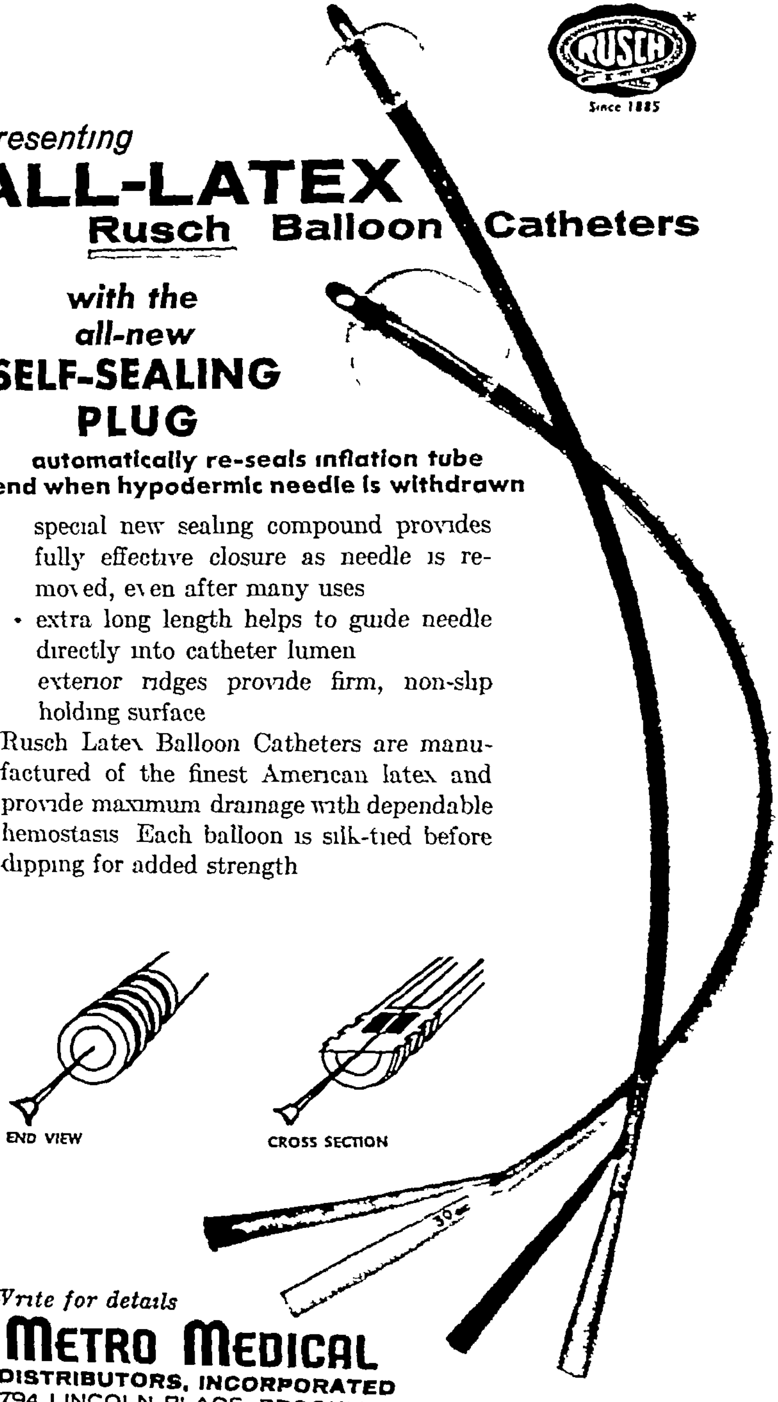

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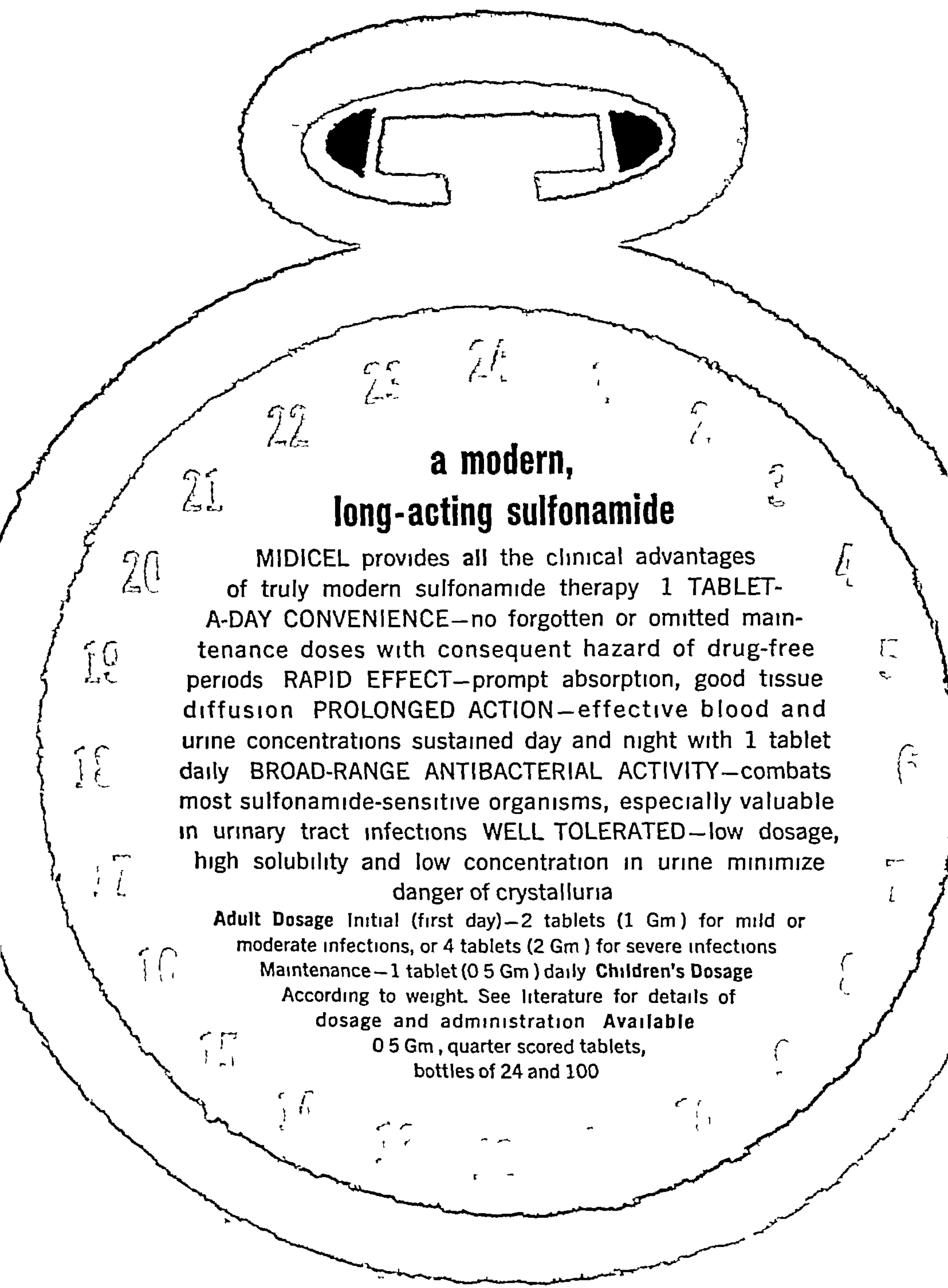

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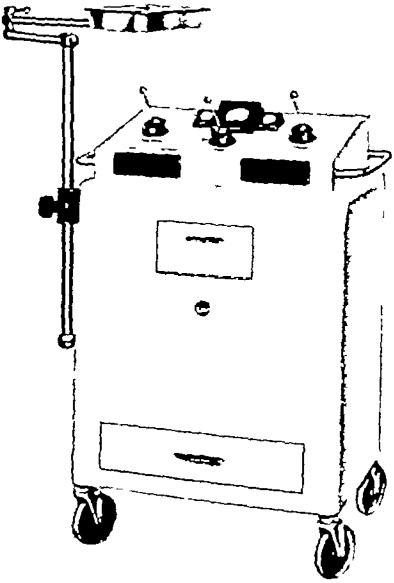

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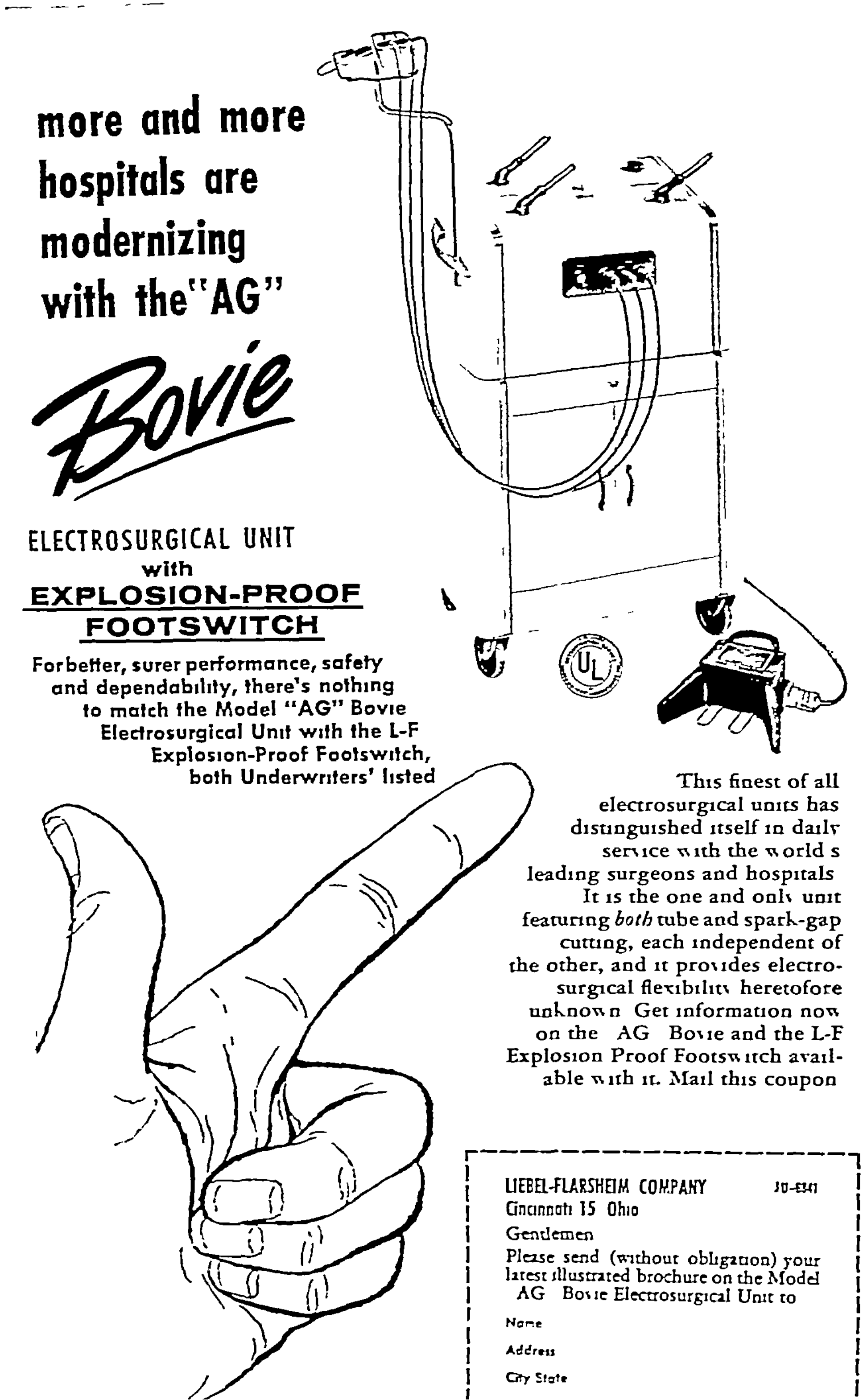

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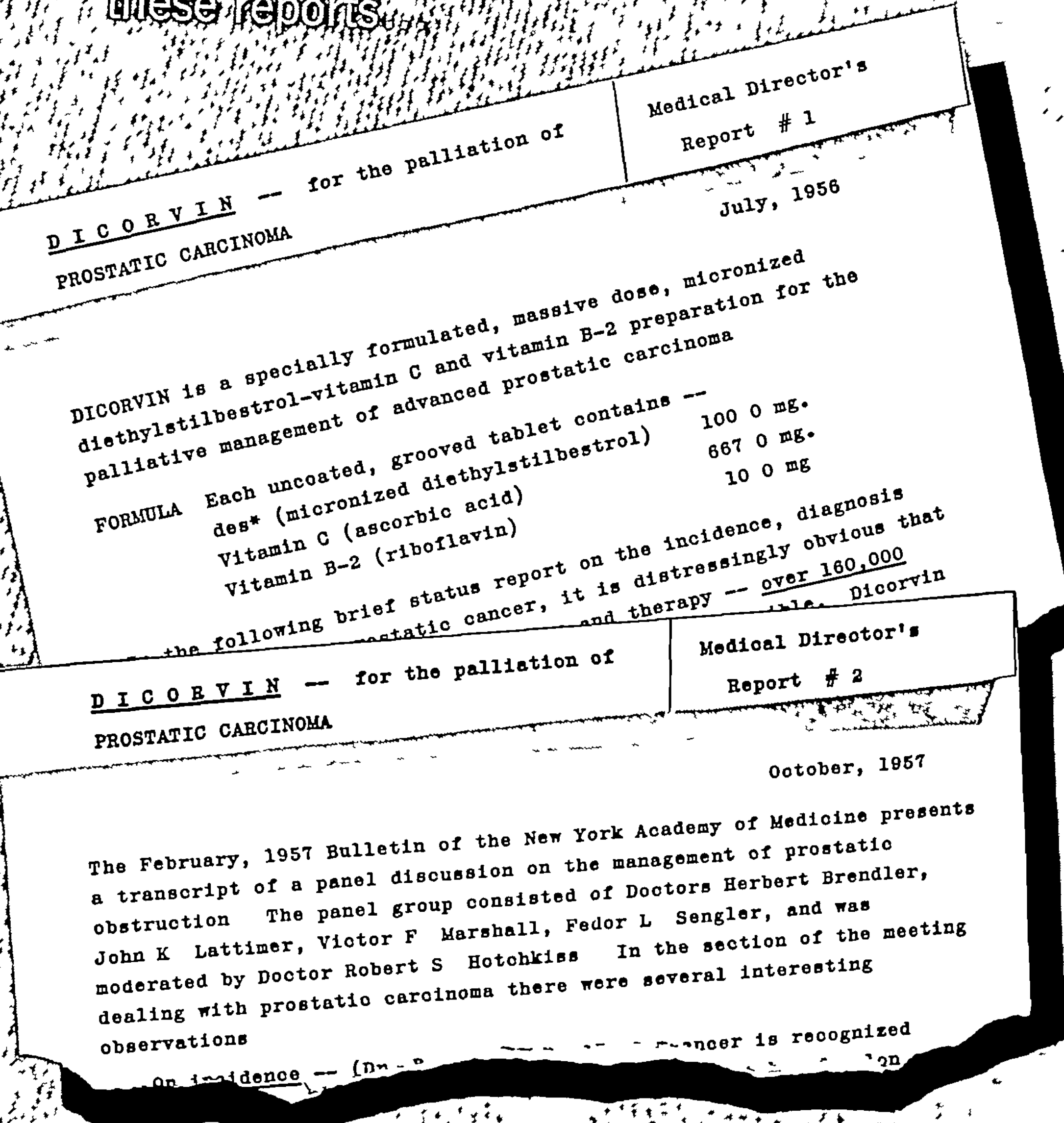

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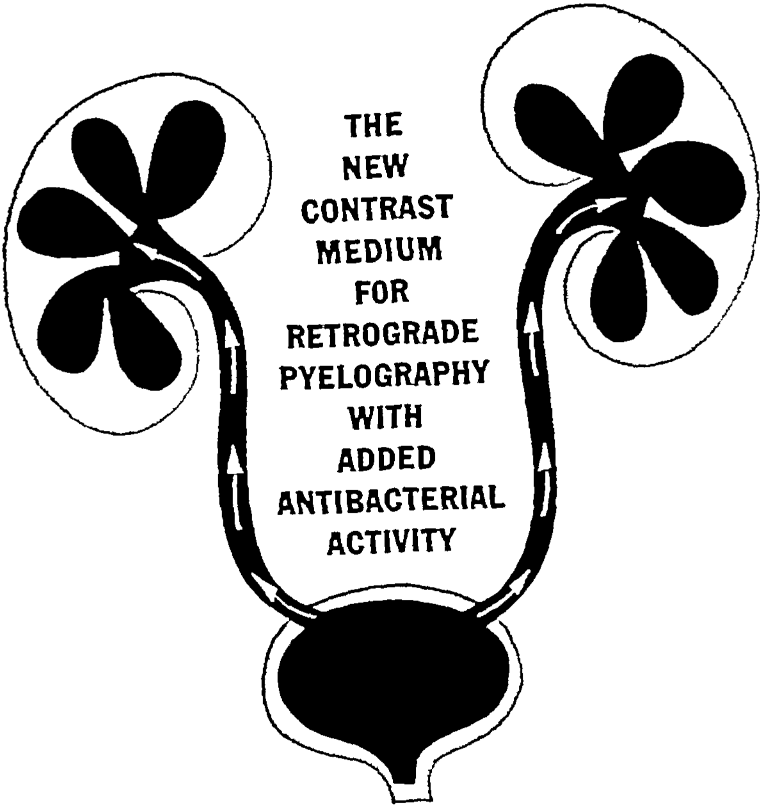

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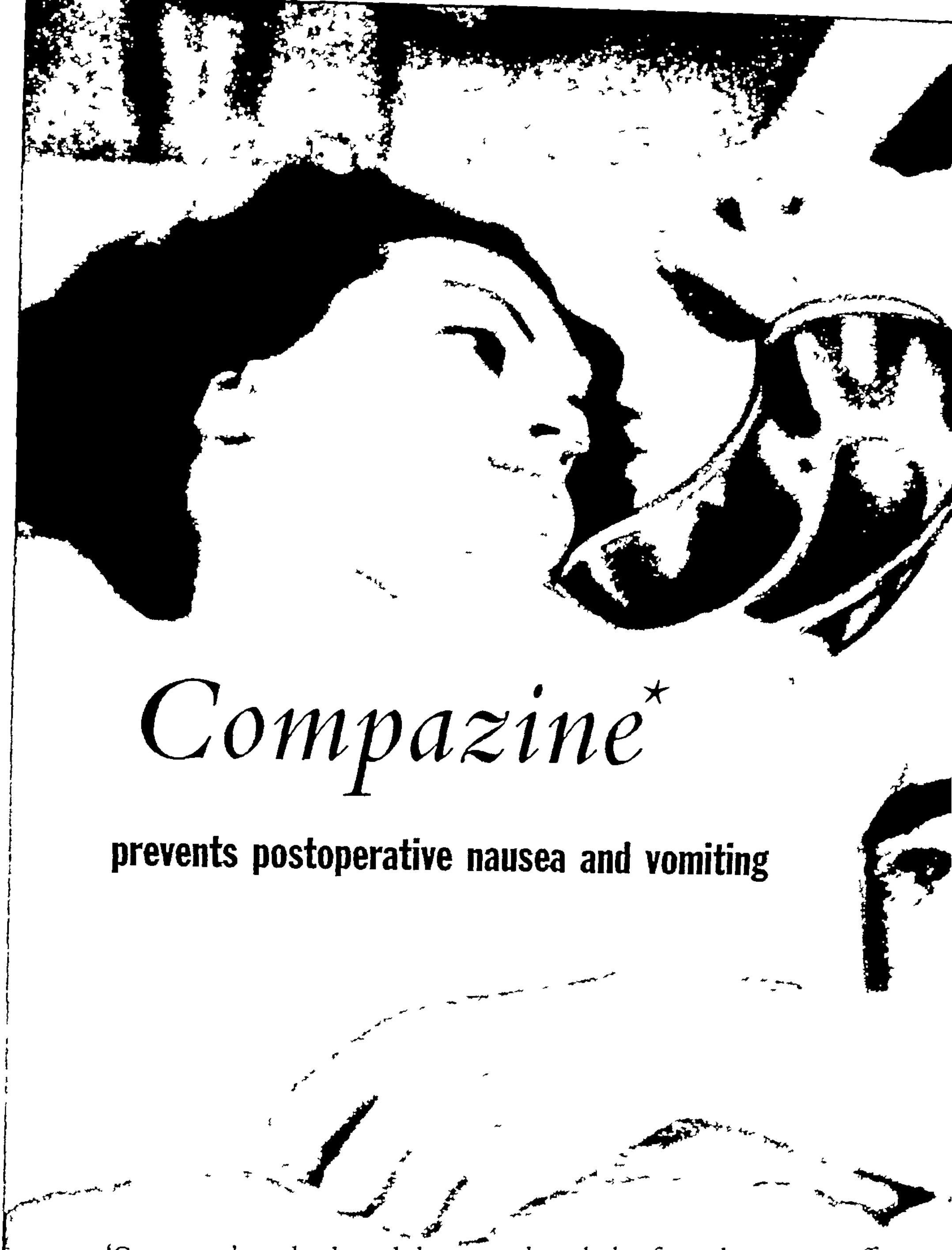

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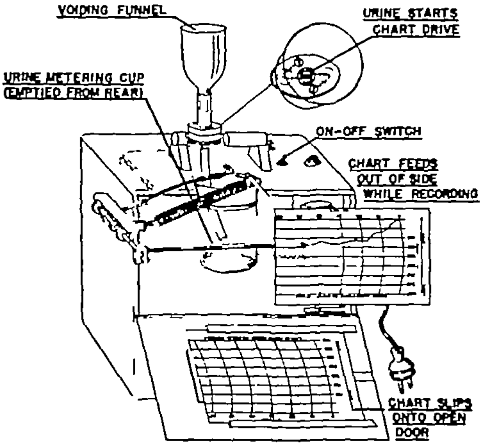
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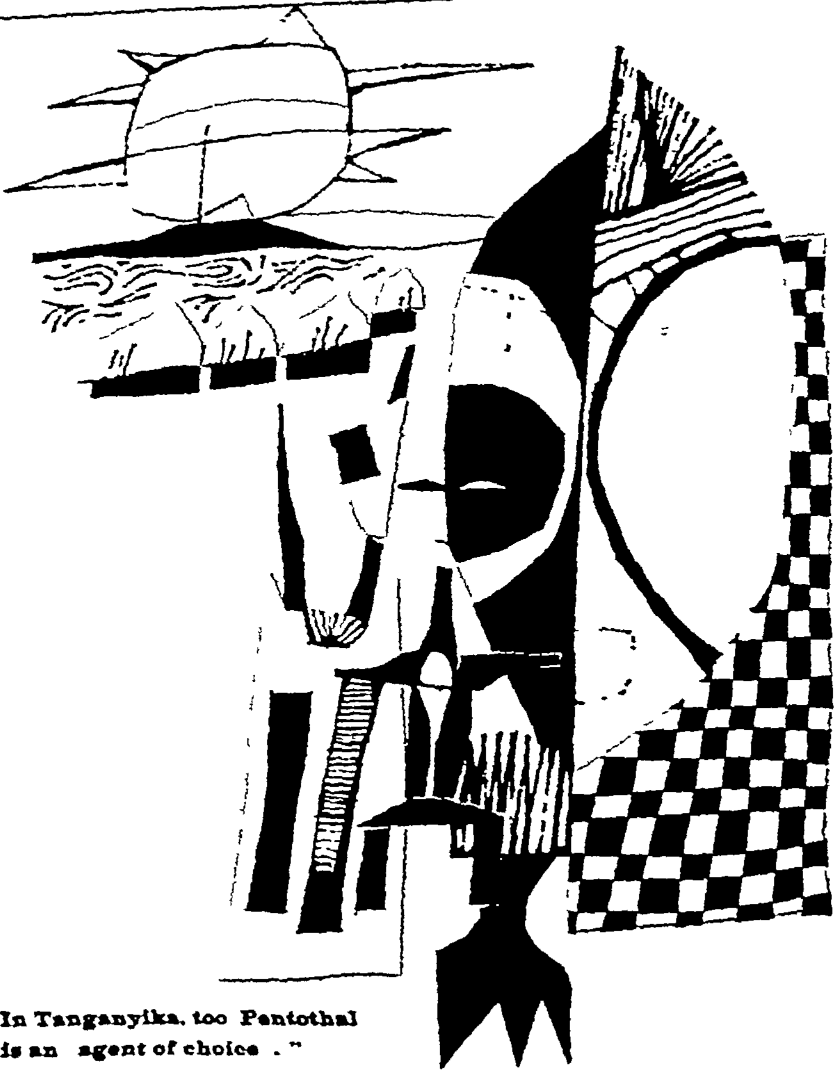

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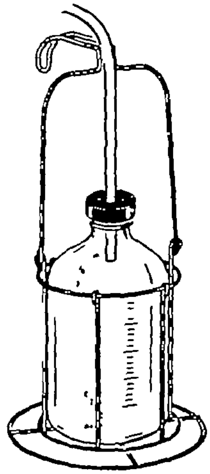
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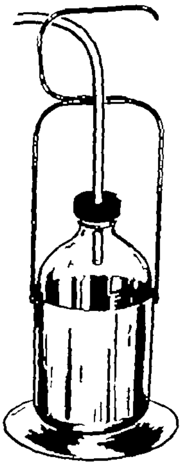
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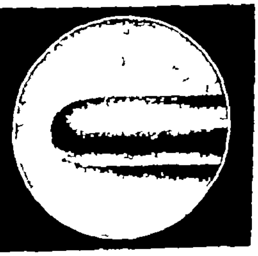

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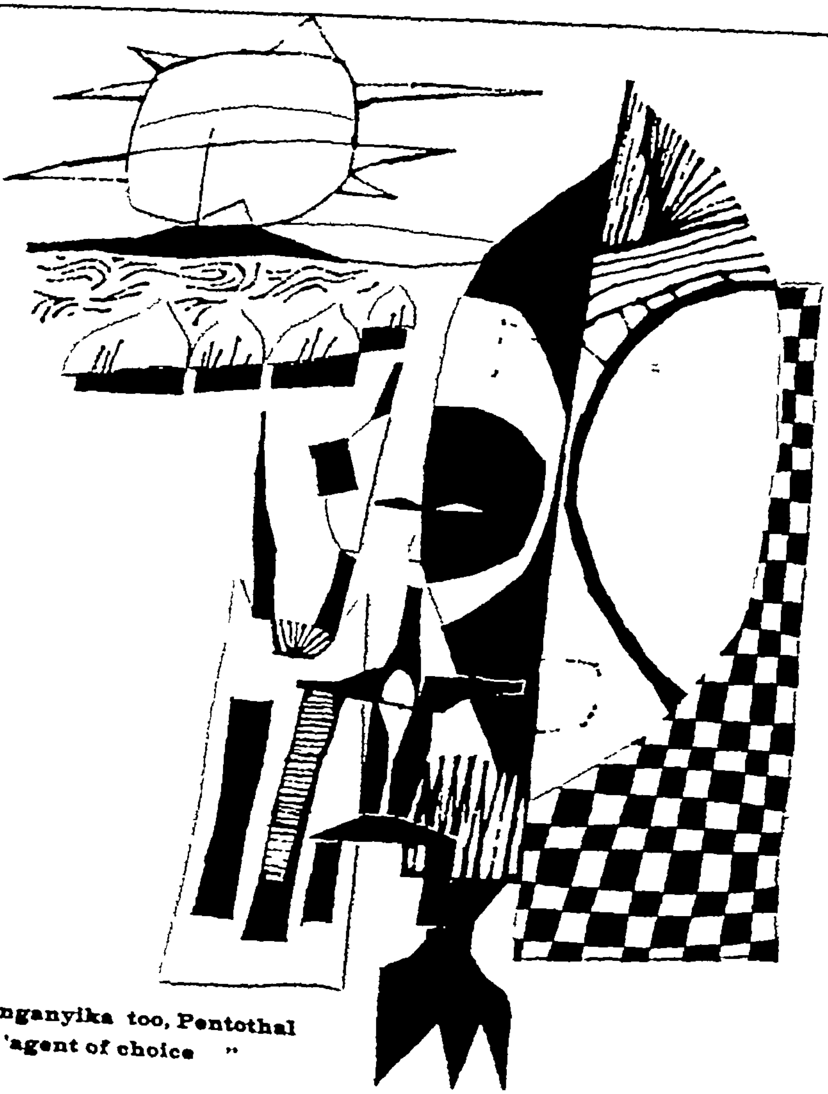

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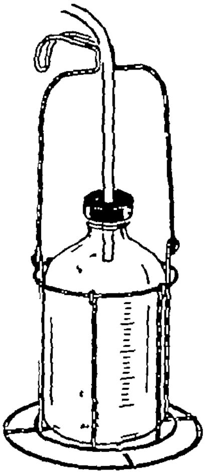

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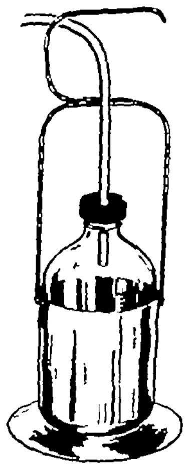

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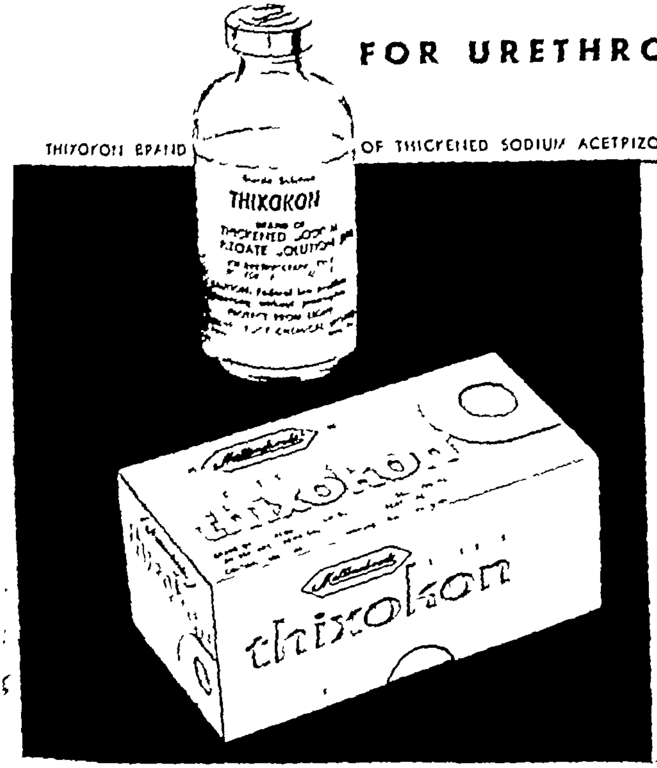

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[1] Vick, N., Campbell, E.W., *Gislason, G.J.*, and Bondi, A.: Sulfaethylthiadiazole (SETD) Therapy for Simple and Complicated Urinary Tract Infections, J. Urol. *77*:777 (May) 1957.

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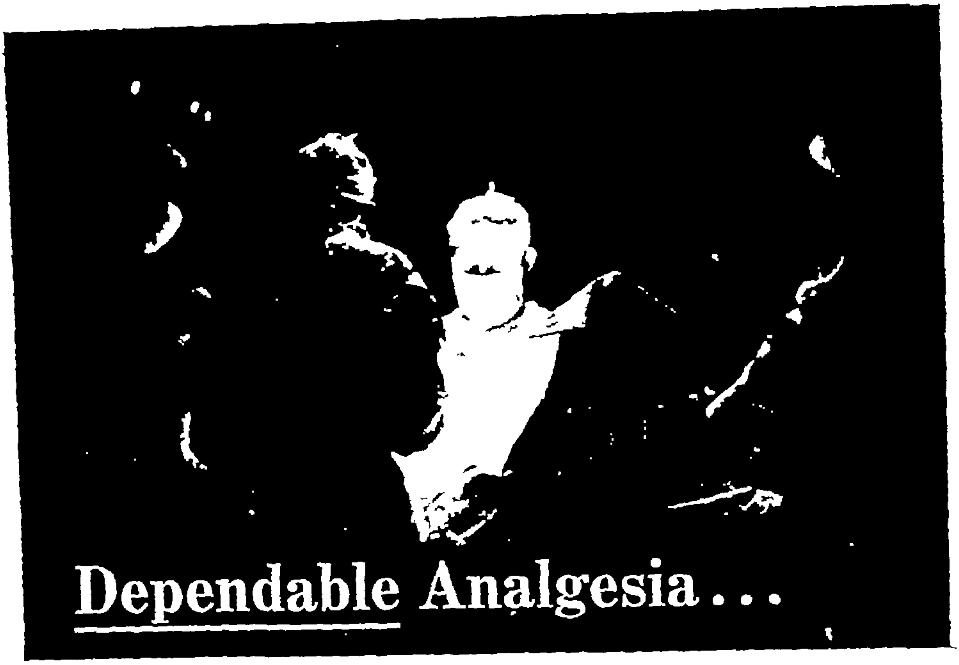

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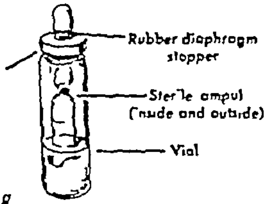

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(1) Flocks, R H , Marberger, H , Begley, B J and Prendergast L J J Urol *74* 549, 1955 (2) Flocks, R H J A M A *163* 709 (Mar 2) 1957

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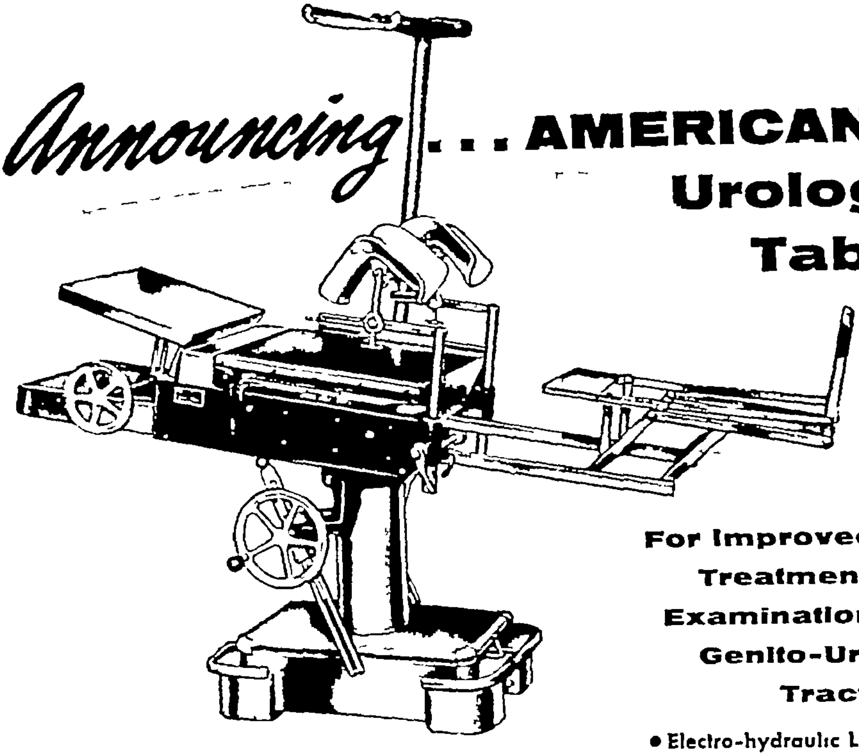

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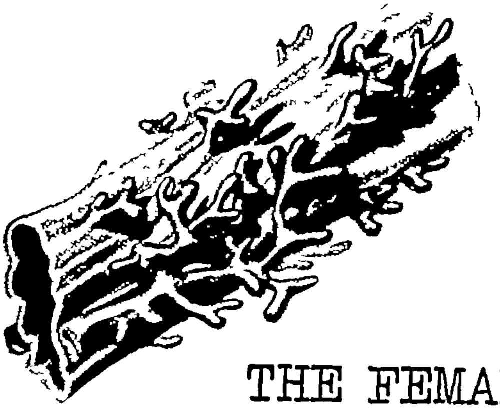

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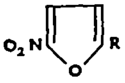
1 Wharton, L R in Campbell M Urology Philadelphia and London W B Saunders Company 1954 vol 2 p 1390 et seq
2 Barrett M E J M Ass Alabama 26 144 1956
3 Youngblood V H J Urol Balt 70 926 1953



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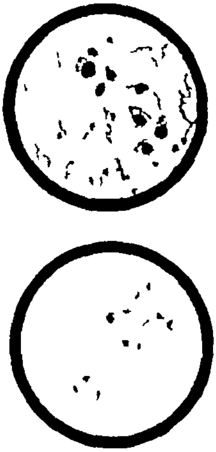

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postmenopausal urethritis .

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4 Youngblood V H Tomlin E M Williams J O and Kimmelstiel P Tr Southeast Sect Am Urol Ass (to be published) 5 Youngblood V H Tomlin E M and Davis J B J Urol Balt 78 150 1957

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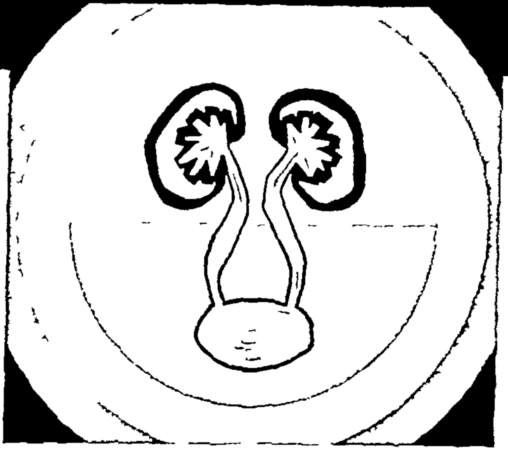

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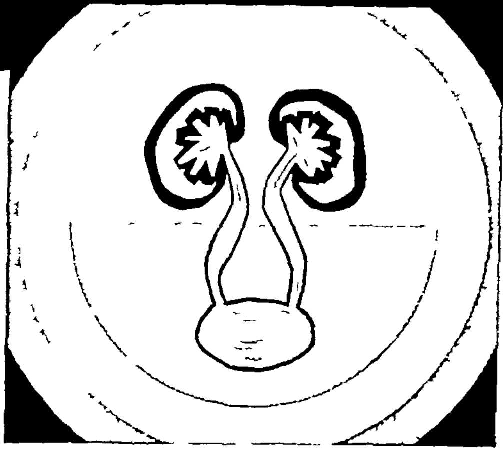

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[1] [illegible] Reed Editorial [illegible] and Its Contribution to Urology The American Journal of Roentgenology 75 775 (Nov 1956)

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"Infertility may often be the only or earliest manifestation of either incipient **Hypothyroidism** or **The Hypometabolic Syndrome** (euthyroid hypometabolism, non myxedematous hypometabolism, metabolic insufficiency, or pseudohypothyroidism) "

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Kupperman, H S , et al The Modern
Endocrine Approach to the Management and
Diagnosis of the Infertile Patient
Scientific Section of 106th Meeting
of A M A New York, N Y , June 3 7 1957

Smith Kline & French Laboratories, Philadelphia

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References:

1 O Conor V J and Sokol J K Quart Bull Northwest U M School 26 161 1952 2 Carroll G and Brennan R V J A M A 157.581 1955 3 Smith P G et al J Urol 65 886 1951 4 Politano V A and Alyea E, P TACE Symposium 1952 5 Headstream J W Trans South Central Sec Am Urol Assoc 1954 6 Mortensen H M J Australia I 728 1953

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often rapidly effective.

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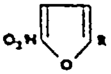

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Triple Sulfonamides, Wyeth
(Trisulfapyrimidines Sulfadiazine
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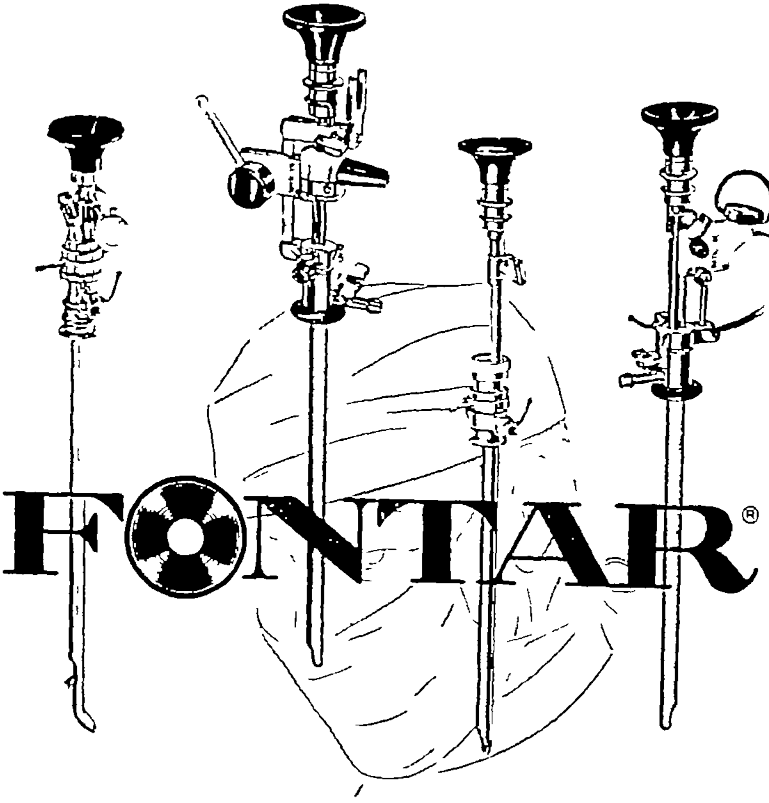

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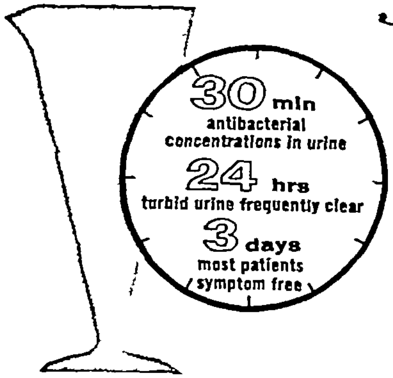
30 min
antibacterial concentrations in urine
24 hrs
turbid urine frequently clear
3 days
most patients symptom free

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for rapid eradication of infection

In the majority of 112 cases of acute persistent or relapsing urinary tract infections "nitrofurantoin [FURADANTIN] was effective clinically, with a pronounced improvement, indicated by the appearance of the urine as well as by verbal commendation by the patient within 24 to 36 hours Some of these patients with seemingly impossible cases were cured of their infection '*

FURADANTIN *first* because of these advantages a specific for urinary tract infections rapid bactericidal action negligible development of bacterial resistance nontoxic to kidneys liver and blood forming organs

AVERAGE DOSAGE *ADULTS*—four 100 mg tablets daily, 1 tablet during each meal and 1 on retiring with food or milk In acute uncomplicated infections 50 mg q.i.d. may be prescribed If patient is unresponsive after 2 to 3 days increase dose to 100 mg q i d

CHILDREN—5 to 7 mg per Kg (2 2 to 3 1 mg per lb) per 24 hours

SUPPLIED Tablets 50 and 100 mg Oral Suspension (25 mg per 5 cc tsp)

*Stewart B L and Rowe H J J Am M Ass 160 1221 1956

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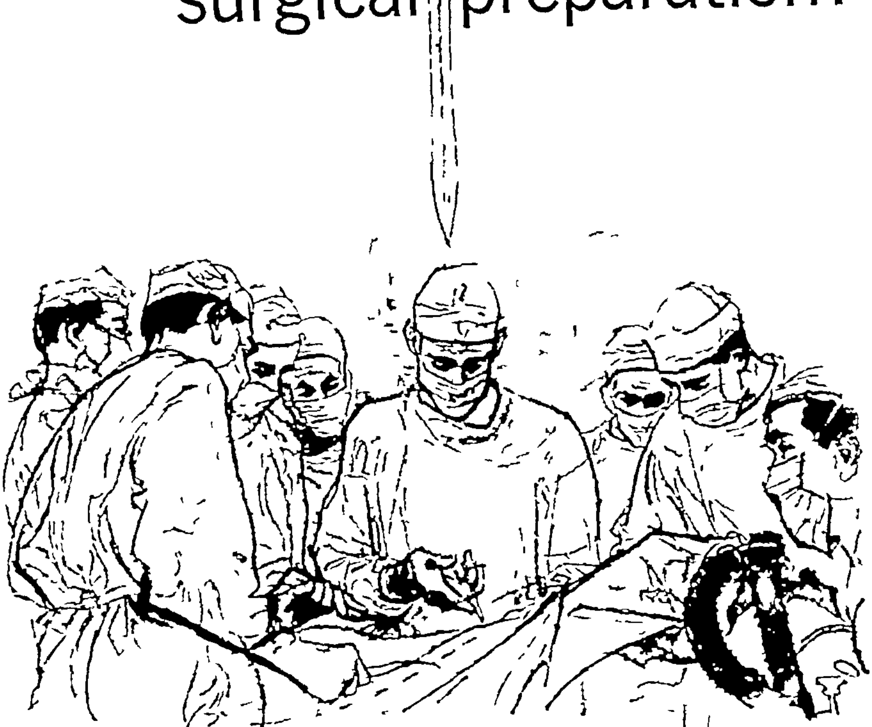

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for cold sterilization

of ☐ heart lung machines
☐ artificial kidneys
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☐ nylon sutures
☐ stainless instruments

Effective against resistant organisms T B., Staph., Proteus, Yeasts and molds, Spores
Non toxic even without rinsing

REF Wolinsky E. Smith, M M and Steenken Wm Jr Tuberculocidal Activity of Clorpactin. A new Chlorine Compound Antibiotic Medicine 1 39 351 July 19[illegible]

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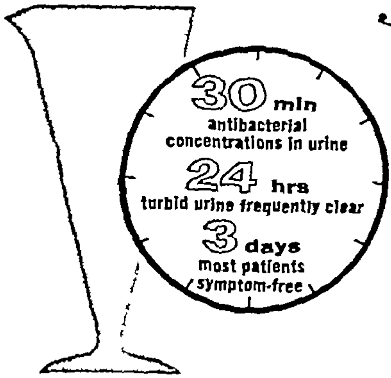

30 min
antibacterial concentrations in urine

24 hrs
turbid urine frequently clear

3 days
most patients symptom-free

FURADANTIN® first...

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CHILDREN—5 to 7 mg per Kg (2 2 to 3 1 mg per lb) per 24 hours

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*Stewart B L and Rowe H J J Am M Ass 160 1221 1956

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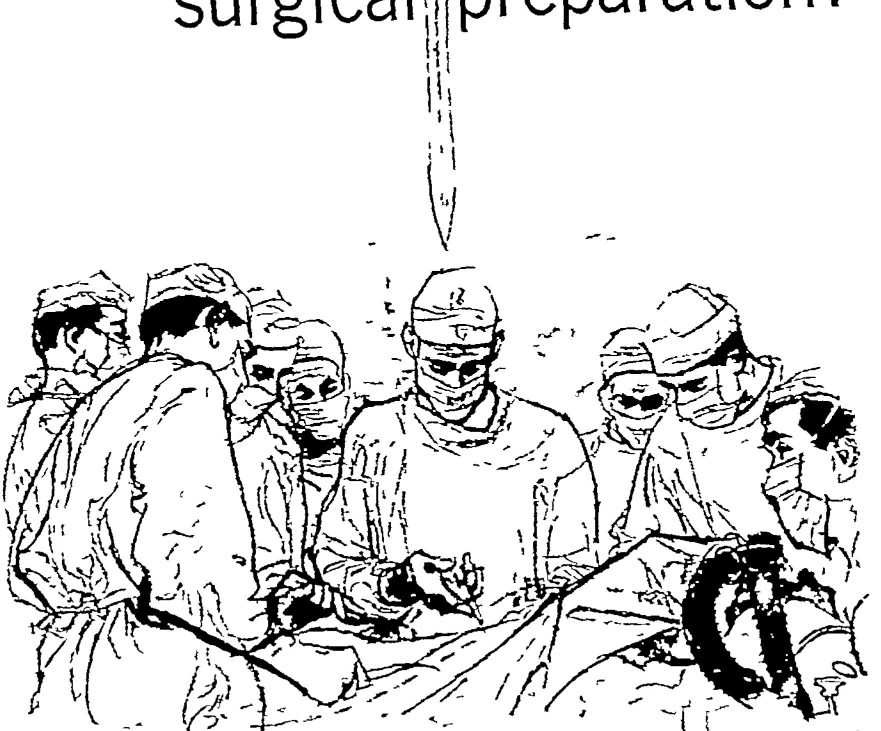

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REF Wolinsky E. Smith, M. M. and Steenken, Wm. Jr Tuberculocidal Activity of Clorpactin. A new Chlorine Compound, *Antibiotic Medicine* 1:352 354, July 1955.

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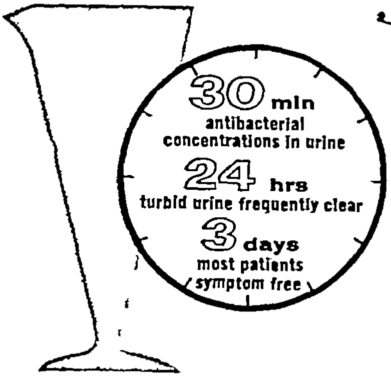

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1 Creevy C D *Surgery 39 180 188 (Jan) 1956*
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*Lowsley O S., and Kirwin, T J *Clinical Urology* Baltimore The Williams & Wilkins Company 1956 p 618

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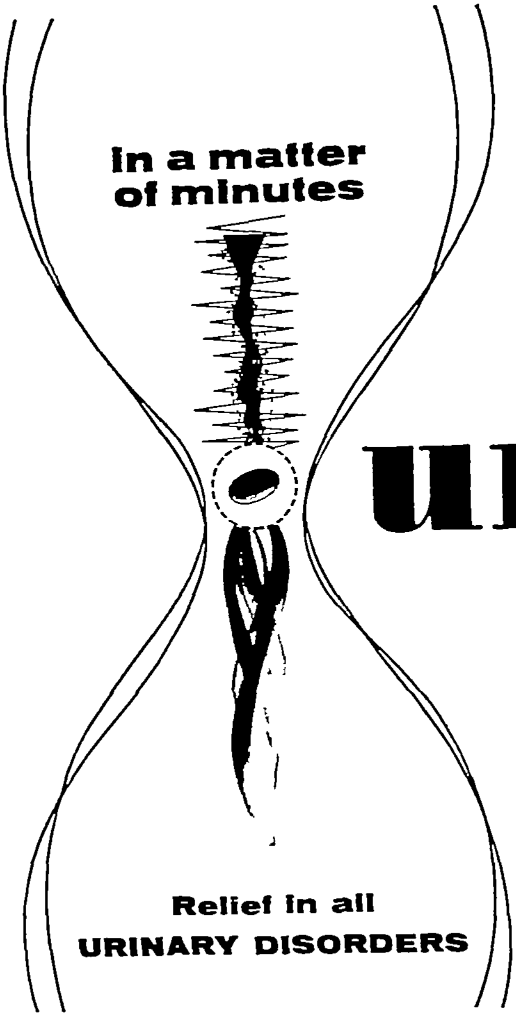

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[1] Strauss, B., Clin. Med., Vol. IV No 3, 1957

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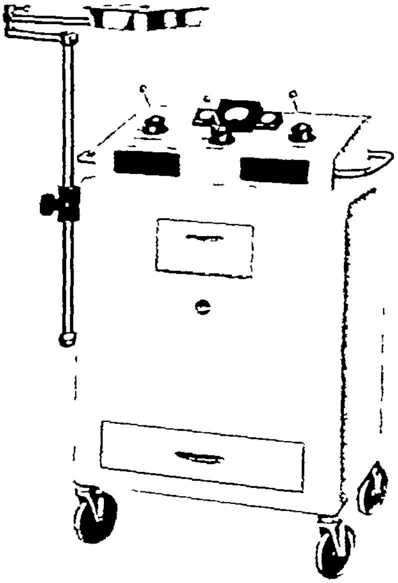

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References 1 Ann Int Med 44 1182 (June) 1956 2 Current Med Dig 20.27 (Sept) 1953

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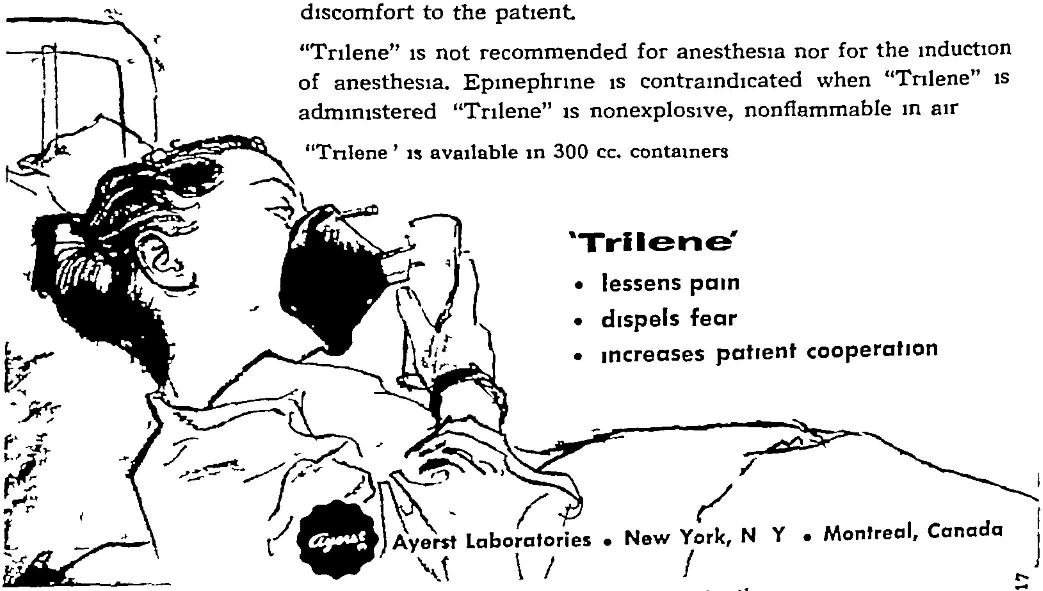

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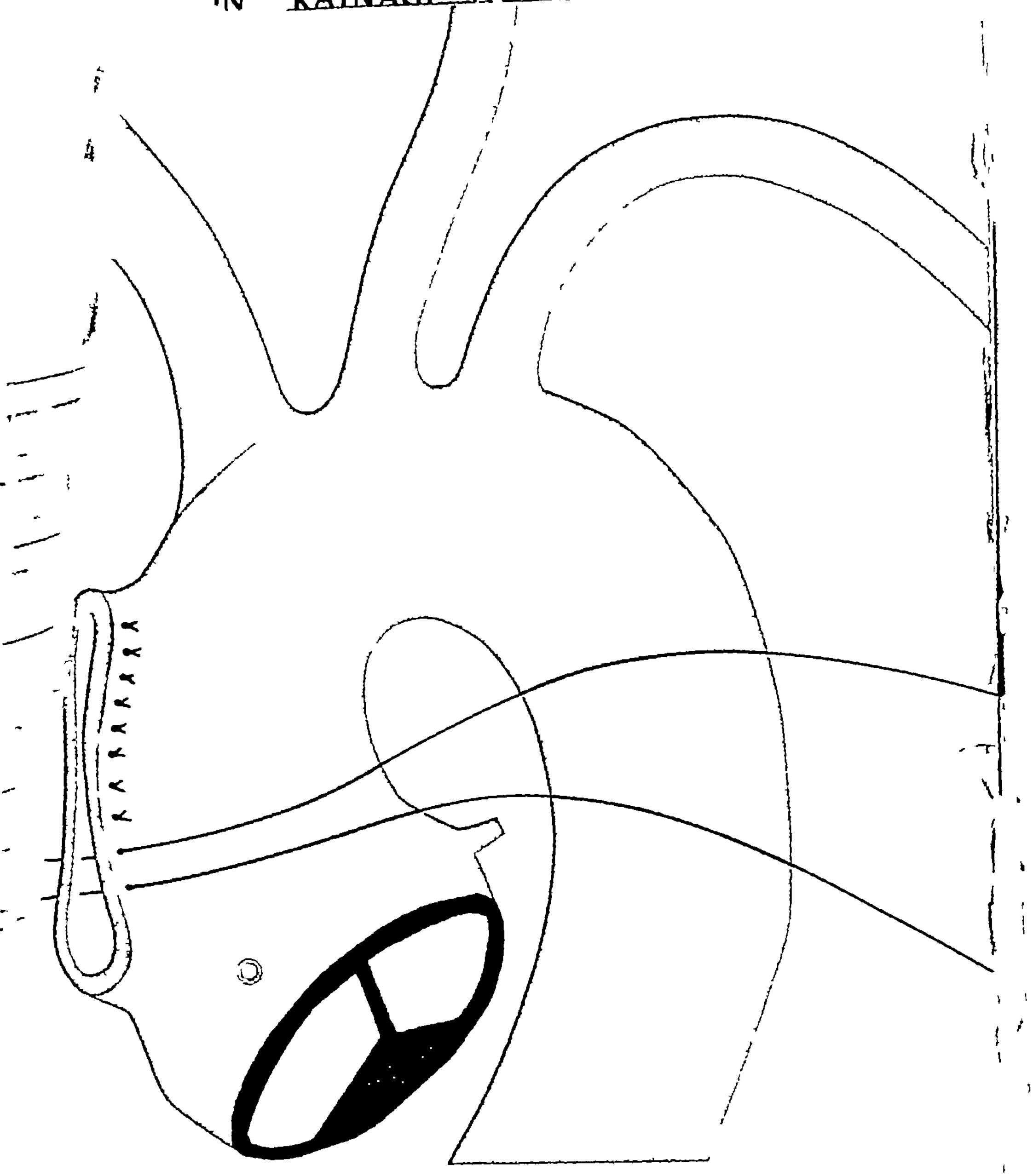

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AID FOR MEN WITH CANCER OF PROSTATE ANNOUNCED

Potent New Product Promises Greater Pain Relief for Larger Number of Sufferers with Incurable Cancer of the Prostate

New York, July 30 — A new product for the relief of advanced cancer of the prostate was announced today by Amfre-Grant, Inc. A representative of the company stated that this new product, called Dicorvin, might well be said to "leave no stone unturned" of present medical knowledge and research by offering the most effective and modern agent possible to provide a longer, pain-free, useful life to the 160,000 sufferers in the incurable stage of this disease.

It was pointed out that although at least one of the ingredients of Dicorvin has been used extensively in cases of cancer of the prostate — the extremely high dosage of this ingredient in Dicorvin goes to work much more quickly and safely because of the special purification and refinement process used in its manufacture It was emphasized that Dicorvin will not cure prostatic cancer — it is a more potent painkiller, and may even slow the advance of the disease At the same time, it has shown a remarkable lack of undesirable side effects — one of the drawbacks of most drugs previously used. Dicorvin, a tablet, is taken by mouth one to three times a day

With this new product, a great many sufferers from cancer of the prostate — usually men past 50 who are beginning to look forward to retirement — may lead relatively normal lives, free from the terrible pain that very often accompanies this type of cancer It may keep many afflicted men alive and comfortable several extra years— possibly long enough to see a cure for their now incurable disease

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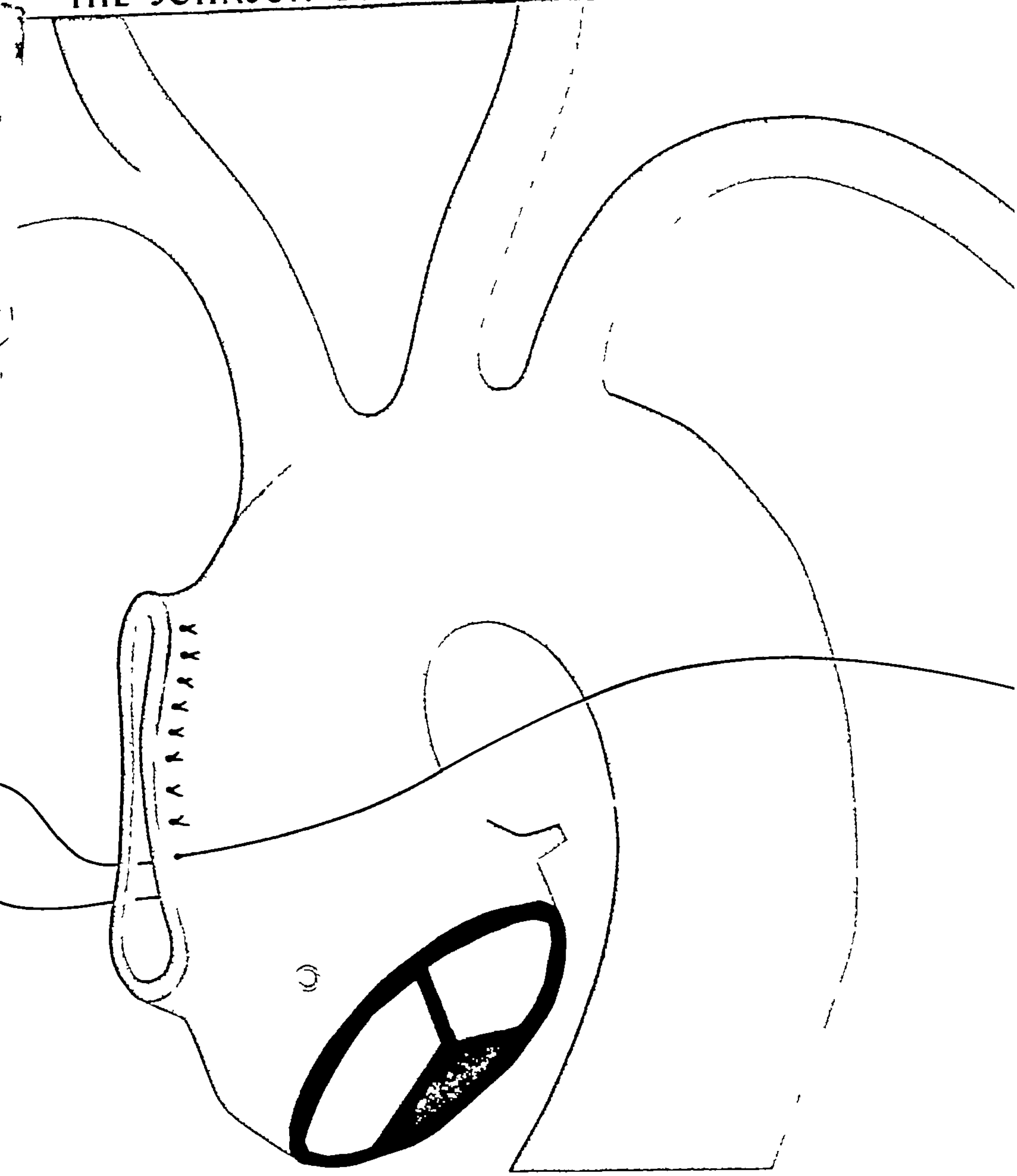

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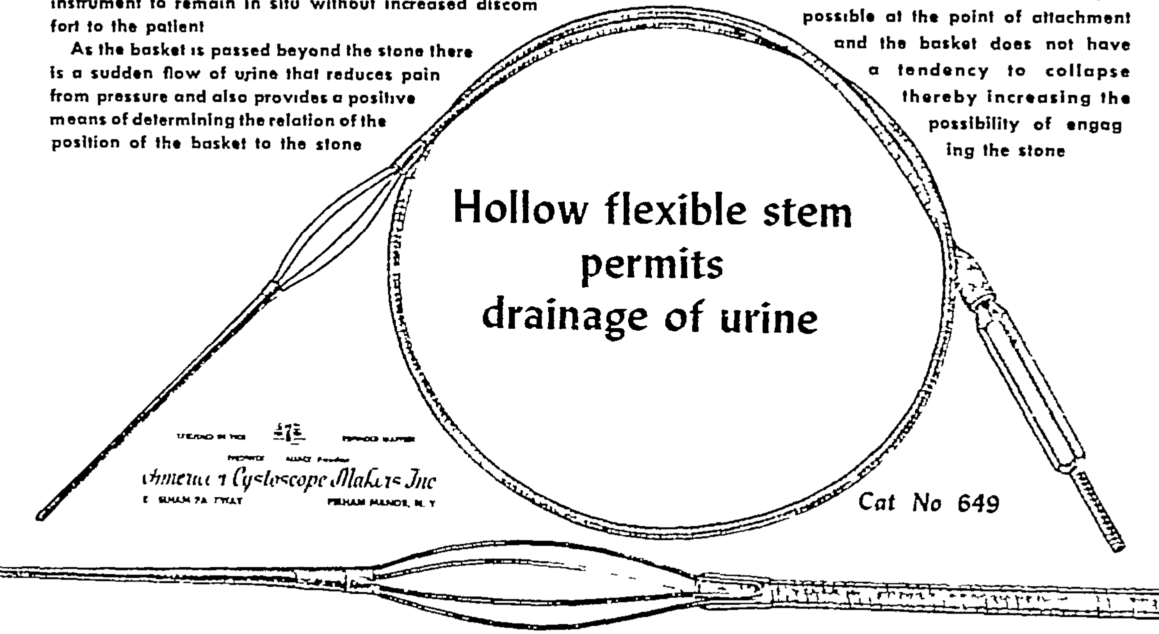

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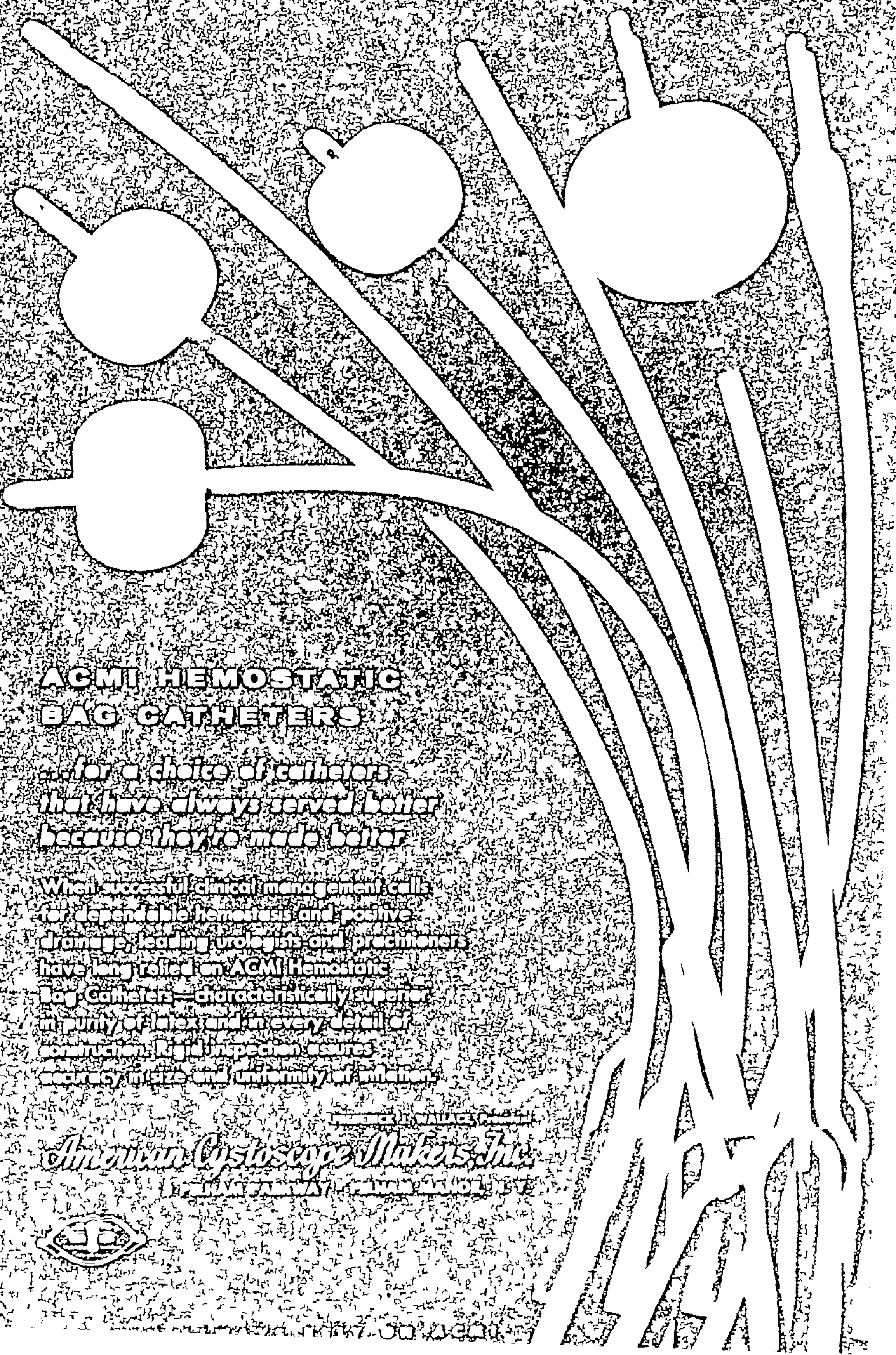

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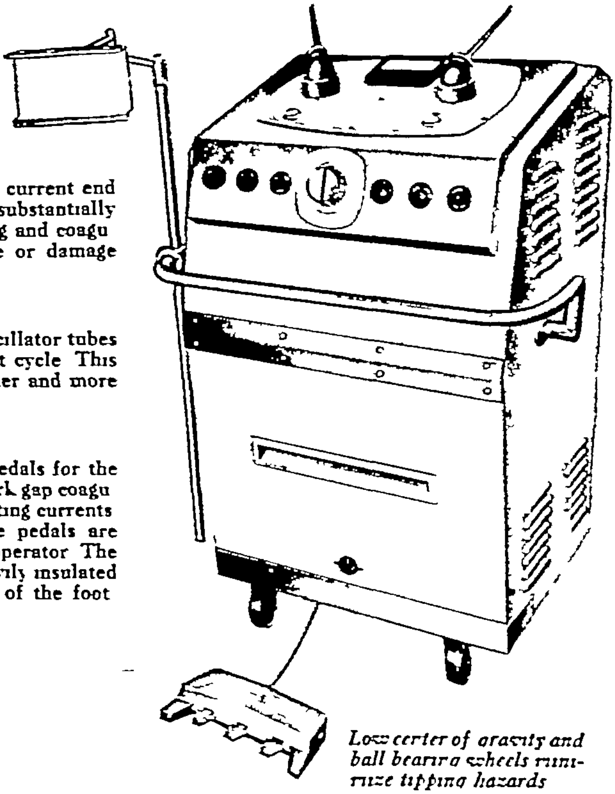

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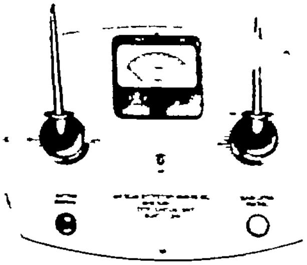

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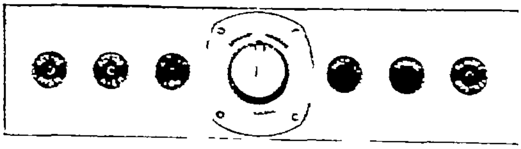

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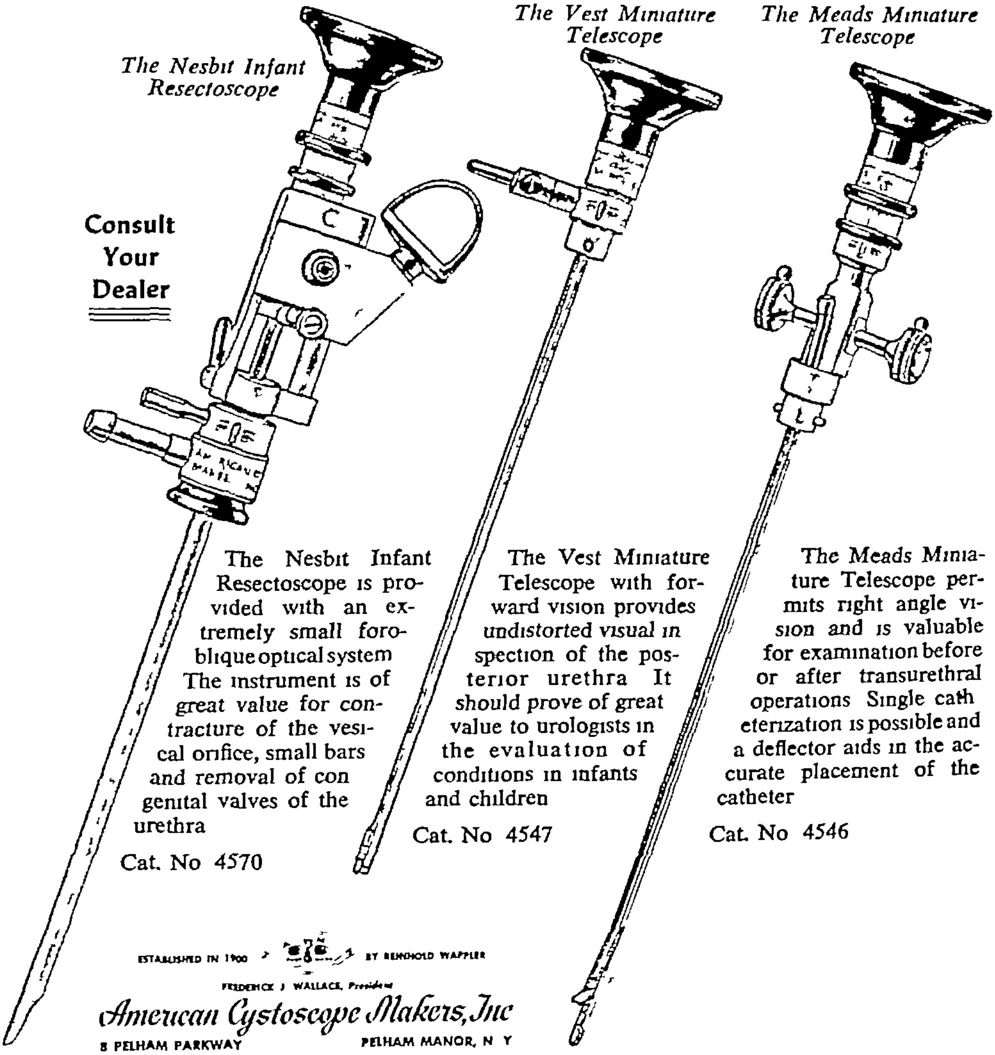

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The Journal of Urology
Vol. 79, No. 2, February 1958
Printed in U.S.A.

A NOTE ON PHEOCHROMOCYTOMA AND RENAL HYPERTENSION

J. HARTWELL HARRISON, FRANK HERBERT GARDNER AND GUSTAVE J. DAMMIN

From the Departments of Genito-Urinary Surgery, Medicine and Pathology, Harvard Medical School, and the Peter Bent Brigham Hospital, Boston 15, Mass.

It seems appropriate at this time to report an unusual instance of renal hypertension due to unilateral renal disease discovered one year after the removal simultaneously of three pheochromocytomas from the same patient. It should be emphasized that pheochromocytoma commonly involves the sympathetic ganglia in the region of the renal vascular pedicle and also the adrenal gland. It is possible that in the removal of such a tumor lying in close contiguity with the renal vessels and especially when receiving blood supply from these vessels that the renal artery and vein could be implicated in subsequent cicatricial tissue which might lead to renal ischemia. The latter leads to the elaboration of rennin, a proteolytic enzyme which acts upon one of the serum globulins termed hypertensinogen by Houssay to convert it to the active vasoconstrictor agent hypertensin which causes hypertension. It seems possible also that the vascular lesions pursuant to hypertension produced by pheochromocytoma could also produce such renal ischemia and the development of persistent hypertension on this basis. We have not previously observed this phenomenon, it had not occurred to us that this sequence of events might occur and we are not aware of its having previously been reported. Since the discovery of pheochromocytoma has become increasingly common it seems especially important to call attention to the possibility of this complication occurring either from the primary vascular disease imposed by the pheochromocytoma or by compromise of the renal vascular pedicle in the dissection of a pheochromocytoma growing next to the renal artery. We have had occasion to remove two such tumors from this location in the last year and it is one of these patients described herein.

The present report concerns a single girl, aged 16 years, who at the age of three was found to have polycythemia. She was admitted to the Peter Bent Brigham Hospital in October 1955 for study by the hematologist. The hematocrit was found to be 57, white blood cells 5,300, neutrophils 59, bands 5, eosinophils 2, lymphocytes 33, mononuclears 1. Blood pressure was 266/150. A regitin test resulted in a transitory fall in blood pressure to 125/80. Study of the plasma norepinephrine showed on three determinations (table 1) a level of 9 2, 10 7 and 12 7 gamma per liter of plasma, whereas epinephrine levels were 3 1 8 and 82 gamma per liter of plasma. Detectable amounts of rennin in the peripheral blood were found by Dr. Florence Haynes, this finding subsequently becomes of real significance. Excretory urograms showed normal renal pelves and ureters. The right renal shadow was normal, the left renal shadow exhibited a small convexity mesially in the region of the upper pole of the left kidney. In November 1955 an exploration resulted in the finding and removal of a pheochromocytoma in-

---

Read at annual meeting of the American Association of Genito-Urinary Surgeons, Hot Springs, Va., May 1-3, 1957.

TABLE 1 *Norepinephrine γ/ liter plasma*

Preop	During Op	Postop
9 2	23 4	4 8
10 7	19 5	4 8
12 7	21 9	2 84

Epinephrine γ/ liter plasma

Preop	During Op	Postop
3	2 9	1 2
1 8	4	1 2
82	6 8	1

volving the sympathetic ganglion at L-3 weighing 9 gm , another pheochromocytoma weighing 10 gm involving the sympathetic ganglion at L-1 and receiving blood supply from the renal vascular pedicle and a third pheochromocytoma involving the lower pole of the left adrenal gland also receiving blood supply from the renal vascular pedicle and weighing 2 5 gm Study of these specimens showed the smaller arteries and arterioles to have hyperplastic thickening of the walls This is anatomic evidence of systemic arterial hypertension A lymph node outside the capsule of the second tumor was found to contain tumor cells Simultaneous exploration of the right sympathetic chain and adrenal as well as the pelvis resulted in the finding of no more tumors

The patient had no hypotensive episodes postoperatively and required no substitution therapy with norepinephrine Plasma norepinephrine level fell to 4 8 to 2 8 gamma per liter postoperatively and remained within normal limits thereafter Epinephrine levels postoperatively were 1 2 and 1 gamma per liter of plasma postoperatively and did not rise above normal thereafter The patient's blood pressure remained elevated at somewhat lower levels than preoperatively but was usually in the range of 180/120

She was followed closely during the ensuing year with repeated studies for evidence of pheochromocytoma and all specific tests yielded normal results in this regard However, hypertension and polycythemia continued to persist and the symptoms of hypertension with severe headaches and signs of encephalopathy definitely progressed Continued efforts to control these two conditions medically with serpasil, ansolysin and repeated phlebotomy were without avail The heart remained normal in size and the lung fields clear

She was readmitted to the hospital in December 1956 Repeated determinations of the plasma and urine catecholamines had shown these to remain within normal limits The hypertension no longer responded to regitin

Excretory urograms were made The renal shadow on the right and the renal pelvis were unchanged from the previous year The left renal pelvis and the shadow of the left kidney appeared definitely smaller Cystoscopic examination was then carried out and divided function studies obtained as shown in tables 2 and 3 It is seen that there is a marked discrepancy in the volume of urine produced simultaneously by the two kidneys, the volume from the left kidney being much less than that from the right Under conditions of normal hydration 20 ml of urine were collected from the right kidney in 10 minutes and this showed a sodium concentration of 28 meq/L Simultaneously the volume of excretion from the left kidney was 3 ml and the sodium concentration measured 10 meq/L Intravenous phenolsulfonphthalein appeared in 3 minutes in excellent concentration from the right kidney and in 15 minutes in only trace amounts from the left kidney The total 10-minute collection from the left kidney could not be measured and that from the right kidney measured 6 per cent These determinations were made on December 11, 1956 This examination was repeated on December 29, 1956 under conditions of forced hydration with a water load These findings are presented in detail in table 3 It is seen again that there is a discrepancy in the function of the two kidneys both as regards quality and quantity of urine excreted From the right kidney in 15 minutes 26 ml were collected containing 1 3 meq/L of sodium as over against only 2 ml from the left kidney with 4 6 meq/L These findings would indicate that under circumstances of water loading the right kidney was able to reabsorb and conserve sodium normally whereas the left kidney was much less able to conserve sodium under the circumstances of severe diuresis which indicates that the tubules of the left kidney are more independent of the normal mechanism of aldosterone sodium retention These findings have been confirmed in the laboratory by Berliner in the presence of induced renal ischemia

In the patient under consideration again the phenolsulfonphthalein excretion was excellent from the right and a greatly diminished excretion from the left occurred in small volume The phenolsulfonphthalein excretion was less on the left than one would have expected from the excretory urograms made a short while before

TABLE 2 *Renal function studies (December 11, 1956) Hydration normal*

	Vol 10	Na/meq/L	P.S.P Appt. T	P S.P 10
R U U	20 ml	28	3′	6%
L U U	3 ml	10	15′ (trace)	—

TABLE 3 *December 29, 1956 Forced hydration water load*

	Vol. 15	Na/meq/L	P S P Appt. T	P.S.P 15
R U U	26 ml	1 3	3′	26 ml 2%
L U U	2 ml	4 6	7′	3 ml 0 3%
Bladder	106 ml	2 2	3′	100 ml 17 %

TABLE 4

Renal Roentgenograms	Preop 1955	Postop 1956
Right kidney length	14 cm	14 cm
Right kidney width	6½ cm	7 cm
Left kidney length	12 cm	9 cm
Left kidney width	6 cm	3½ cm

Significant data are obtained from a detailed study of the renal roentgenograms listed in table 4 Measurements of the renal shadows on these films show that in 1955 the right kidney was 14 cm in length and 6½ cm in width In 1956, one year later, these measurements are the same for the right kidney The left kidney in 1955 was 12 cm in length and 6 cm in width, whereas one year later in 1956 the left kidney was only 9 cm in length and 3½ cm in width These measurements are also supported by the diminution in size of the renal pelvis as demonstrated by excretory urography With retrograde pyelography the discrepancy was less owing to the overfilling of the left renal pelvis but it is still apparent that there has been a marked diminution in renal mass in one year accompanied by progressive hypertension Both kidneys had appeared to be normal at operation in 1955

Since no evidence of residual pheochromocytoma could be found and since such positive evidence of unilateral renal disease on the left was present, exploration of the left kidney was planned with the intent of putting in a renal arterial graft if this seemed feasible according to the technique of Poutasse and associates or of removing the left kidney A unilateral sympathectomy was planned because of the severity of the patient's hypertension and the desire, if possible, to save her one additional operation If hypertension were not relieved by the renal surgery and if unilateral sympathectomy had been carried out the patient would then need only one further operation to complete a bilateral sympathectomy Accordingly, on January 4, 1957, a transthoracic exposure of the left kidney was accomplished The kidney was found to be encased in dense scar tissue and to be even smaller than had been estimated by measurements of the roentgenographic shadows The renal vascular pedicle was exposed and no localized area of constriction was found However, the entire left renal artery was small from the kidney to the aorta The renal parenchyma was so thinned and irregular that there was no question regarding saving this kidney Prior to nephrectomy 50 cc blood was drawn from the renal vein for rennin determination This was found to be markedly elevated by Dr Florence Haynes There was also some elevation of the rennin level of the peripheral blood There was no evidence of any residual pheochromocytoma or adrenal gland on this side Nephrectomy was completed without incident and simultaneously a unilateral thoracolumbar sympathectomy was performed by Dr Francis D Moore The patient's blood pressure fell from levels of 200/100 to 160/85 pursuant to the nephrectomy Postoperatively the patient's blood pressure fell to 100/80 and it was necessary to maintain her tension by means of neosynephrine drip for 2 days During convalescence the blood pressure stabilized at 120/80

The pathologic report follows The kidney weighed 52 gm and had a thick capsule which was adherent to the subjacent parenchyma The subcapsular parenchyma was finely granular, suggestive of atrophy There were several depressed areas which proved to be partially healed infarcts At one pole the largest of these infarcts was found and represented an area on the cut surface of about 1 by 2 cm Except for the infarcts which were only partially organized, the cortex was uniformly atrophied and contracted to a thickness of 3–4 mm

There were no gross alterations of the medulla There was hyperemia of the pelvic mucosa which also had scattered petechiae

The most proximal portion of the renal arteries appeared grossly normal However, there was prominence of the smaller branches, namely the arcuate arteries and those supplying the infarct at one pole appeared to be occluded The veins appeared normal

Microscopically the cortical atrophy was uniform and of advanced degree affecting as usual the tubular portions of the nephron primarily The infarcts still had glomeruli recognizable in some degree and probably represented an alteration ranging from possibly 1 to 4 months' duration

Several arteries within and outside of the infarcts had thrombi in various stages of organization and would have corresponded to about the same duration as that of the infarcts There was no evidence that there had been an appreciable degree of arteriolosclerosis before the atrophic process had been initiated

Anatomic diagnoses Atrophy of the kidney, advanced (52 gm), multiple small infarcts, partially organized thrombi in tertiary and smaller branches of the renal arteries, partially organized and canalized

DISCUSSION

Two processes must have been responsible for the atrophy and the infarcts This type of uniform atrophy is usually the result of a reduction in renal arterial blood supply near the origin of the renal artery by narrowing of the lumen Microscopically there was no lesion observed in the largest arteries in the sections The thrombi described in the smaller branches, as aforementioned, accounted for some of the larger areas of ischemic necrosis but could not account for the uniform atrophy of the cortex In terms of this patient's course, the infarcts are moderately recent, possibly one to four months in duration It is more difficult to estimate the duration of the diffuse cortical atrophy, except to say that the left kidney appeared normal at operation about 14 months before it was removed and the process might have had a duration almost as long as this interval but this alteration could have taken place in a shorter period of time Either lesion and both lesions, the infarcts and the diffuse cortical atrophy have been observed as principal lesions in kidneys thought to be the basis of hypertension when these were present as unilateral lesions

Total renal function studies have continued to be within normal limits and three months postoperatively her blood pressure is 120/80 to 130/90 and the hematocrit is maintained at a level of 45 without phlebotomy This case will be reported with others in detail with especial reference to both hormonal, hematologic and pathologic studies including the details of intensive followup examinations This is the second instance in one year of removal of an ischemic kidney resulting in cure of hypertension and diminished polycythemia on this service

SUMMARY

Attention has been called to the possibility of unilateral renal disease causing a persistence of hypertension after the removal of pheochromocytoma The pos-

Significant data are obtained from a detailed study of the renal roentgenograms listed in table 4 Measurements of the renal shadows on these films show that in 1955 the right kidney was 14 cm in length and 6½ cm in width In 1956, one year later, these measurements are the same for the right kidney The left kidney in 1955 was 12 cm in length and 6 cm in width, whereas one year later in 1956 the left kidney was only 9 cm in length and 3½ cm in width These measurements are also supported by the diminution in size of the renal pelvis as demonstrated by excretory urography With retrograde pyelography the discrepancy was less owing to the overfilling of the left renal pelvis but it is still apparent that there has been a marked diminution in renal mass in one year accompanied by progressive hypertension Both kidneys had appeared to be normal at operation in 1955

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METHOD OF INSTITUTING NEPHROSTOMY DRAINAGE IN A DUPLEX KIDNEY (URETEROPYELOSTOMY WITH NEPHROSTOMY)

JOHN J O'CONNOR JR

From Department of Urology St Mary's Hospital Hoboken N J

The problem of establishing nephrostomy drainage in a duplex kidney is rarely encountered Double nephrostomy is technically unsatisfactory and heminephrectomy of the upper pole may either be too extensive a procedure in a poor risk patient or technically not feasible due to blood supply and other factors The following case report and procedure are offered as a simple solution to a vexing problem

CASE REPORT

E R (No 22430) A 56-year-old white woman was admitted to St Mary's Hospital on September 19, 1956 complaining of profuse painful leakage of urine and feces through the vagina of two months' duration In January 1952 the patient underwent total hysterectomy for carcinoma of uterine cervix Postoperatively radium irradiation was given (dosage unknown) In 1955 the patient was treated elsewhere with radioactive cobalt for recurrence of carcinoma in vaginal vault Approximately ten months following this the patient noted onset of vaginal leakage of both urine and feces

Temperature 98 6F Pulse 96 Respiration 24 Blood pressure 164 84 The patient was in obvious distress No abdominal masses were felt Pelvic examination disclosed that architectural pattern of the vagina was totally deformed by scar tissue No tumor masses were felt Urine and feces leaked per vaginam

Laboratory studies Hematocrit 33 per cent white blood count 9,000/cu mm Urinalysis cloudy, specific gravity 1 006 albumin one plus, loaded with pus and red cells Blood sugar 143 mg per cent Blood nonprotein nitrogen 34 mg per cent

Cystoscopy was performed September 21 Marked urethral stenosis was dilated Vision in the bladder was too poor for structure delineation Methylene blue inserted into bladder appeared in anterior fornix of vagina Intravenous urography on September 25 revealed delayed function on the right with marked hydronephrosis (fig 1) No dye was visualized on the left side in 30 minutes and one hour A catheter was left indwelling in the bladder and urinary leakage was controlled for several days then recurred in copious amounts Because of the severe discomfort caused by vesicovaginal and rectovaginal leakage, colostomy and right nephrostomy were decided upon

On October 4 through a routine lumbar incision the right kidney was exposed and an unexpected complete duplication of the renal pelves and upper ureters was found (fig 2 A) It was felt that a double nephrostomy was a poor solution to the problem and that heminephrectomy was too extensive a procedure The

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sibility of coincident pheochromocytoma and unilateral renal ischemia producing hypertension is noted and it is emphasized that the dissection and removal of pheochromocytoma particularly in the region of the renal vascular pedicle may be followed by such a complication If the blood pressure does not return to normal after removal of the pheochromocytoma the importance of intensive investigation of renal function with separate determinations of volume, sodium and phthalein excretion is emphasized Repeated roentgenograms of the kidneys will detect decrease in the size of renal parenchyma and pelvis Aortography with renal arteriograms will demonstrate the vascular changes earlier as shown by Poutasse and associates Rennin determinations of the peripheral blood may be suggestive of primary renal hypertension under these circumstances

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On October 4, through a routine lumbar incision the right kidney was exposed and an unexpected complete duplication of the renal pelves and upper ureters was found (fig 2, *A*) It was felt that a double nephrostomy was a poor solution to the problem and that heminephrectomy was too extensive a procedure The

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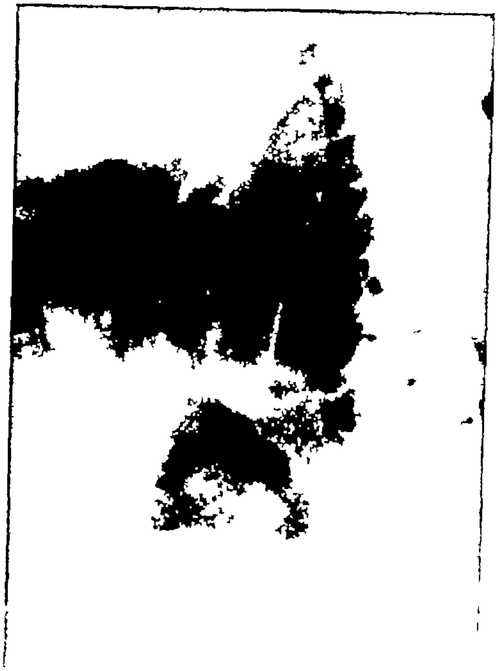

FIG 1 Thirty minute preoperative intravenous pyelogram

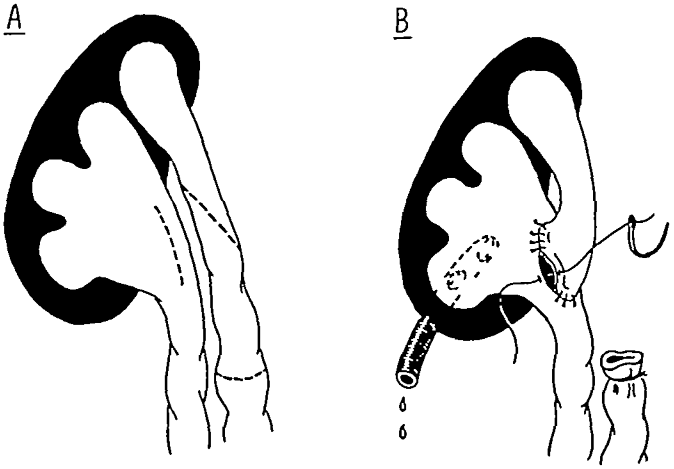

FIG 2 *A*, duplex kidney Dotted lines show lines of incision *B*, schematic representation of procedure

lower pelvis was then opened on its anterior surface and a size 26F whistle tip nephrostomy tube placed through the lower pole The upper ureter was then transected diagonally and the distal portion excised The bevelled end was then sutured to the lower pelvis incision with interrupted 4-0 atraumatic chromic catgut (fig 2, *B*) A rubber drain was inserted and the wound closed in the routine manner

The position of the patient was changed and a difficult loop colostomy was performed in the left lower quadrant The pelvis was markedly infiltrated with scar and tumor

The right kidney put out two liters per day of clear urine There was slight drainage by way of the Foley catheter in the bladder, it being assumed that drainage came from left kidney It was planned to do a left nephrostomy as soon

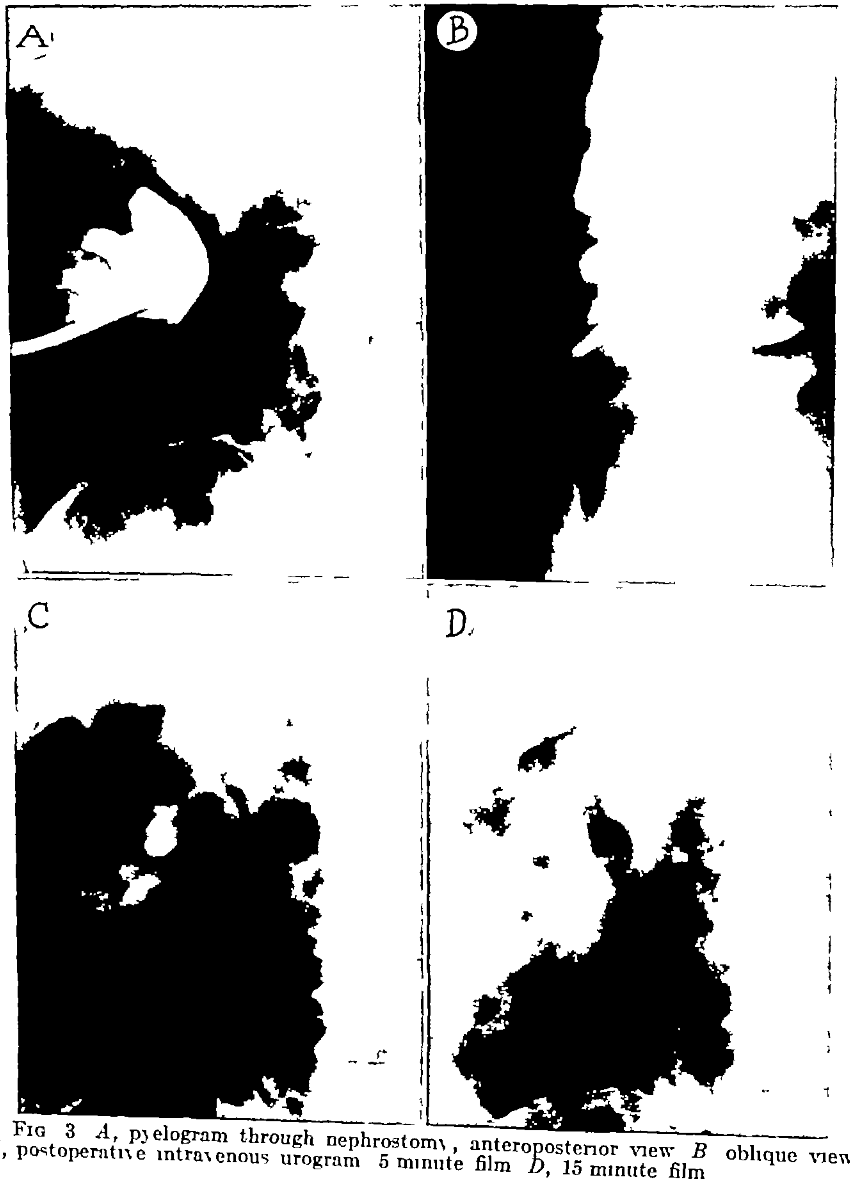

FIG 3 *A*, pyelogram through nephrostomy, anteroposterior view *B* oblique view *C*, postoperative intravenous urogram 5 minute film *D*, 15 minute film

as the patient's condition permitted Unfortunately it was noted on the third day that the colostomy wound was grossly infected and that the loop was retracting beneath the skin level On the sixth postoperative day nephrostomy pyelogram and intravenous pyelography were done The former showed marked decrease in hydronephrosis and the anastomotic site was beautifully demonstrated in the anteroposterior (fig 3, *A*) and oblique (fig 3, *B*) views The intravenous pyelogram showed prompt good function (fig 3, *C* and *D*), again with marked reduction in hydronephrosis and demonstrating patency of anastomosis The colostomy was opened the seventh day The stoma gradually retracted beneath skin level and eventually this wound totally broke down The situation was worsened because the function of the left kidney increased and once again the patient leaked urine per vaginam in spite of successful nephrostomy on the right The patient slowly went downhill and expired November 23

DISCUSSION

The basic concepts in ureteropyelostomy are not new Thomas Moore[1] in 1948 presented an excellent review of the literature on transureteroureterostomy and presented the first case of true transureteropyelostomy in which the result was excellent At the time of surgery in the case presented, ureteropyelostomy in a duplex kidney had not been reported in the American literature However, in March 1957 Gibson[2] reported essentially the same procedure for ureteral ectopia with satisfying results The case herein presented shows another useful application of this technique In spite of the eventual demise of the patient, the procedure proved completely satisfactory for the local problem The main advantages are 1) ease of execution, 2) elimination of second nephrostomy tube, and 3) avoidance of the more extensive heminephrectomy of the upper renal pole

SUMMARY

A case of ureteropyelostomy and nephrostomy in a duplex kidney is presented The procedure is reported as a simple and satisfactory answer to an unusual problem

2124 New York Ave , Union City, N J

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[1] Moore, T J Urol , 60 859, 1948

[2] Gibson, T E J Urol , 77 414 1957

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MESONEPHROMA A UROLOGIC PROBLEM

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From The DePuy Sorkness Clinic, Jamestown, North Dakota
AND ARTHUR K SAIKI
From The University of North Dakota School of Medicine, Grand Forks, North Dakota

It is our purpose to present a concise review of the literature concerning the problem of persisting mesonephric tissue in the adult female and to present a case report in which persisting mesonephric tissue constituted a urologic problem This latter situation has not been previously described in the literature available to us

A consideration of renal embryology is essential to the understanding of the development and significance of this type of tumor The three developmental stages of the kidney, it will be recalled, are the pronephros, mesonephros, and metanephros

The pronephros disappears, but the more caudal portion, the mesonephros, persists and its duct becomes the wolffian duct The tubules of the wolffian duct reach their maximum development in the fourth week[1] The mesonephric duct empties into the cloaca and later the urogenital sinus[2] The caudal portion of the mesonephros undergoes hypertrophy and is differentiated to form the metanephros, the essential part of a permanent kidney During the third month the mesonephric duct atrophies if a female develops, or changes to become the ductus deferens if a male develops[1] It is with the consequences of failure of this normal regression in the female that we are here concerned

When the ovary passes from the lumbar region to the pelvis, it draws with it the wolffian mesentery which forms the mesosalpinx In the adult the remains of the wolffian duct consist of an ill-defined cord in the mesosalpinx parallel to the fallopian tube as the ductus epoophori longitudinalis Sometimes in children and much more rarely in adults it persists further and reaches the cervix and vaginal mucosa under which it passes to terminate in a small opening at the base of the hymen[1] This vaginal portion constitutes Gärtner's duct A complete wolffian duct in the female will extend from the hymen to the cervix, upwards behind the broad ligament, retroperitoneally, ventral to the ureter, and thence to the superior pole of the kidney where it will terminate between the kidney and the adrenal gland It is suggested[1] that some of the so-called abnormal ureters or extra ureters are in reality persisting wolffian ducts

Controversy exists as to the existence of mesonephromas, especially as ovarian tumors Huffman[3] asserts that mesonephric elements in the ovary have not been described As the ovary increases in size it is gradually pinched

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[1] Greig D M and Herzfeld G On the persistence of complete wolffian ducts in females Edinburgh M J 34 701-724 1927

[2] Novak Emil Woodruff J D and Novak E R Probable mesonephric origin of certain female genital tumors Am J Obst & Gynec 68 1222-1239 1954

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off from the mesonephros As a result the mesonephric epithelial elements are excluded from incorporation in the ovary However, Schiller,[4] while admitting that it probably is inconceivable for ovarian tumors of pronephric and metanephric origin to arise because of lack of topographical relationship in man, does support the possibility of true mesonephric tumors of the ovary He states that the gonads and wolffian body develop in close proximity but are separated by the genital grooves Should the genital grooves be located more peripherally—closer to the mesonephros—the result would be an inclusion of mesonephric elements in the ovary The mesonephric inclusions are probably formed when the wolffian body is in an undifferentiated state Since the gonads develop later than the mesonephros it can be assumed that the cells forming the mesonephric inclusions are laid down in coelomic epithelium, where the gonads subsequently arise Huffman[3] concludes that Schiller's concept has not been proved and that the strongest argument against ovarian tumors arising from mesonephric rests is the fact that benign mesonephric epithelial elements, common elsewhere along the genital tract, are not found in the substance of the ovary

Three basic groups of tumors arising from mesonephric tissue along the genital tract have been described The first group are adenomas and were first described by Meyer[5] in 1897 and 1903 Wolfe,[6] in writing the first American clinical report on the subject in 1940, reported that in 1413 cervices examined in the years 1923–38 at Long Island University College of Medicine, two cases of adenomatoid hyperplasia of mesonephric origin were found In addition one case of the second basic group, adenocarcinoma, was found Huffman,[7] in the second American report in 1948, reported four adenomas and one adenocarcinoma found in 1192 cervices In his paper Huffman[7] presents a résumé listing eight adenomas, six adenocarcinomas, four non-neoplastic fetal elements and two cases of the cystic tumors, the third basic group, described prior to 1948 The seventh case of adenocarcinoma was added by Nace[8] in 1952 Novak and associates report eight cases three benign and five malignant Other reports include Henkel,[9] Campagna and associates,[10] Jones and Seegar,[11] Schiller,[4, 12] Reay,[13] Wright,[14] Tuta and Siebel,[15] Stowe,[16] and Bisca [17]

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[4] Schiller, Walter Mesonephroma ovarii Am J Cancer, **35** 1–21, 1939

[5] Meyer, R Ztschr Geburtsh u Gynak , **58** 527, 1906

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[15] Tuta J A and Siebel J E Malignant mesonephroma of the ovary A M A Arch Path **31** 386–390 1941

Grossly, the tumors are described[4] as soft, friable, of light color and semisolid consistency Microscopically, there are but one or two capillary loops in the so-called glomerular tufts of these tumors Jones and Seegar[11] summarize Schiller's criteria as follows "1) Tumor cells resemble endothelial cells of glomeruli 2) Tumors contain structural units which resemble glomeruli 3) Tubules are found in the tumors 4) These tumors may occur at the site normally occupied by mesonephric remnants" Further description of the histologic appearance of cervical mesonephric remnants is given by Huffman[7] ' that of small tubules lined by a low columnar epithelium of cuboidal cells with translucent cytoplasm and large round nuclei "

The following case of mesonephroma of the right ovary with metastatic obstruction of the right ureter and infiltration of the bladder wall is presented as an addition to the previously reported group of tumors In addition, it is presented as the first reported case to our knowledge of such a tumor being present in the bladder, thus constituting a problem in urologic diagnosis and treatment

A 73-year-old white widow was first seen by one of us (R S W) in January 1956 at which time her complaint was weakness She was found to have a hemoglobin of 55 per cent and an erythrocyte count of 2,840,000 The blood smear showed a macrocytic hypochromic anemia Gastric analysis revealed achlorhydria An upper gastrointestinal study, cholecystogram and barium enema were normal The stool was negative for occult blood A diagnosis of primary anemia was made, and she was successfully treated with vitamin B-12 injections and got along well until September 1956 when she noted dysuria frequency and pain over the bladder Her urinalysis showed a trace of albumin and 6–10 leukocytes per high power field She was placed on an antibiotic and her symptoms subsided

She was next seen in November 1956, at which time she gave a history of having been quite sick and treated by her local doctor for a urinary tract infection Her urine at this time showed 3 plus albumin, and it was loaded with leukocytes and showed 8–15 erythrocytes per high power field Her weight was stable, hemoglobin 65 per cent and she felt fairly well She was advised to continue with her local doctor s treatment

She was next seen on January 3 1957 at which time she had lost 10 pounds, her hemoglobin was 52 per cent and she was complaining of right flank pain A urinalysis was normal.

Hospitalization was advised, and she entered Jamestown Hospital on January 6 1957 with the chief complaint of constant right flank pain of one week's duration

Physical examination revealed a patient who gave evidence of weight loss Her weight was 153 pounds, blood pressure 106/68 temperature 101F, pulse 80 per minute, respirations 14 per minute Examination revealed grey hair, false teeth and a pale conjunctiva There were no palpable nodes in the neck The

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[16] Stowe L M On the genesis of the so-called mesonephroma ovarii Cancer 8 446–453, 1955

[17] Bisca B V Mesonephric remnants in the adult female Obst & Gynec, 8 265–269, 1956

chest was clear to auscultation and percussion The heart tones were good and no enlargement of the heart was noted on percussion The abdomen was normal except for pain on percussion over the right flank Bimanual examination of the pelvis revealed a normal cervix and adnexae The corpus was atrophic No edema was noted and the skin was quite pale in color

Admission laboratory work included a urinalysis which revealed an acid reaction, specific gravity of 1 014, a faint trace of albumin, and was negative for sugar Microscopic examination revealed an occasional pus cell The hemoglobin was 8 6 grams or 55 per cent, the erythrocyte count was 2,460,000 per cu mm , the leukocyte count was 10,050 per cu mm , and the erythrocyte sedimentation rate was 85 mm per hour

X-rays of the lumbosacral spine revealed a mild degree of osteoporosis and osteoarthritis

An intravenous urogram showed the renal shadows to be normal in size There was slow excretion of the dye into both pelviocalyceal systems but there was good concentration There was incomplete filling and rather marked dilatation of the calyces on the right The right ureter was not visualized

On January 10, 1957 cystoscopic examination revealed the presence of two ulcerated lesions with rolled elevated edges in the bladder, one medial to the right ureteral orifice and 1 0 cm in diameter, and one above the right ureteral orifice and 2 0 cm in diameter Ureteral catheterization on the right side met obstruction at about 15 0 cm and no urine was recovered from this catheter Contrast medium was injected by gravity and the report was as follows "Con-

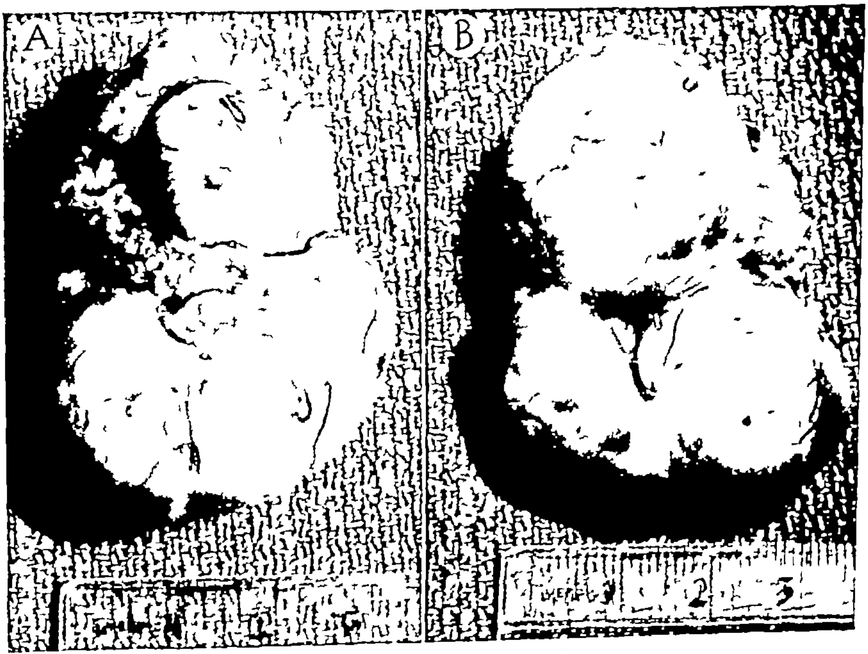

FIG 1 Resected right ovarian tumor

trast medium can be traced as far as the first sacral segment Here it is sharply demarcated The possibility of an infiltrative process in this region is considered A portion of the ureter is visualized above this point and demonstrates kinking There is again evidence of marked hydronephrosis on the right "

On January 12, 1957 the lesions in the bladder were resected transurethrally and their bases fulgurated

A pathologic diagnosis of mesonephroma was made from these specimens The gross and microscopic report follows

"Gross A number of fragments to a centimeter in greatest diameter of firm grey-white to grey-yellow tissue, some of which has a slightly papillary configuration Segments of ureter are not grossly identified

Microscopic These fragments present a rather interesting microscopic picture In some of the fragments there is almost solid epithelial proliferation, the cells of which vary moderately in size, some containing relatively abundant clear cytoplasm In other fragments, in addition to the solid epithelial proliferations, a number of tubular formations are seen resembling tubules of the kidney In still other fragments are structures mimicking glomeruli This picture is consistent with mesonephroma Diagnosis—Mesonephroma (fig 2, *C*) "[15]

The pathologists also made the following remark "This tumor shows a remarkably good reproduction of the tubules and glomeruli Such tumors are usually malignant and this one is definitely malignant, and believed to have arisen from remnants of mesonephric duct along the urogenital ridge on the right side "[15]

Subsequent to this the patient received a total dosage of 4702 roentgen units of deep x-ray therapy to the anterior and posterior pelvis

Because of the rapid downhill course of the patient x-ray therapy was stopped The flank pain subsided, and she began to gain strength and vigor following transfusions of whole blood

In late February and early March, the patient began to complain of pain and began to lose appetite and weight

At laparotomy on March 15, 1957 a solid lobulated tumor of the right ovary weighing 30 gm was removed (fig 1) The tubes, left ovary and uterus were atrophic and freely movable There was evidence of some infiltration retroperitoneally on the right side in the region of the mid ureter The pathologic description follows

"Gross A 5 5 by 3 0 by 2 5 cm smooth surfaced, slightly lobulated ovarian mass Several small up to 8 mm in diameter slightly raised cystic areas are noted beneath the capsule On section the solid portion is composed of grey-white firm tissue with a slightly yellow tinge In areas it is somewhat honeycombed with a microcystic appearance Sections through the cystic areas reveal several cysts up to 8 mm in diameter that are filled with opalescent gelatin-like material Tumor does not extend through the ovarian capsule

Microscopic Numerous sections through this specimen show variegated

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[15] Saiki A K Personal communication, University of North Dakota School of Medicine Department of Pathology

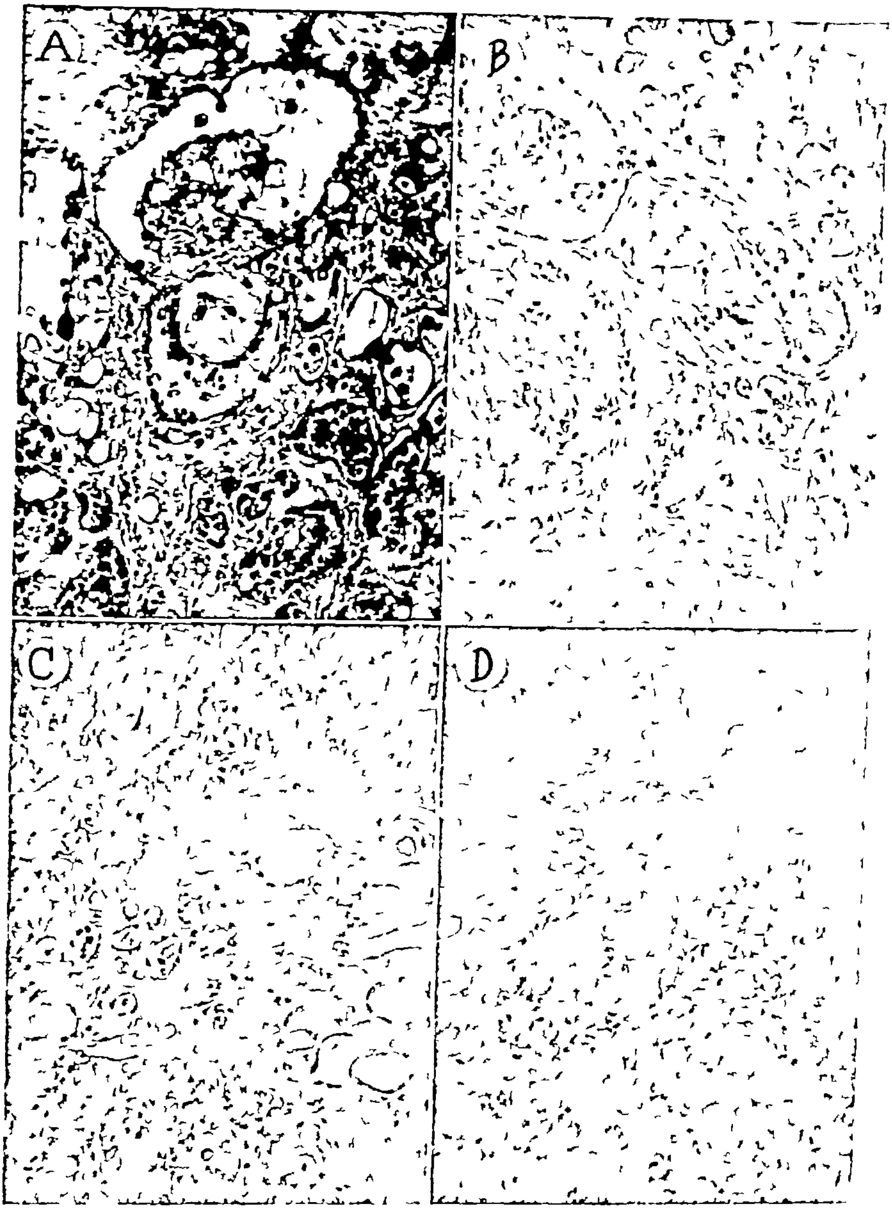

FIG 2 *A*, *B*, *D*, photomicrographs of right ovarian tumor *C*, photomicrograph of bladder tumor Courtesy of Dr Theodore Snook University of North Dakota School of Medicine

areas of epithelial proliferation In some areas the tumor cells form solid sheets of cells which are poorly differentiated and in other areas are many structures simulating glomeruli with other areas showing attempt at reproduction of the tubular structures This tumor is interspersed with many areas of necrotic changes Only stromal remnants are seen of the ovary Diagnosis Mesonephroma of the right ovary (fig 2, *A*, *B*, *D*)"[18]

The patient died in the middle of August 1957, and an autopsy was done Metastases of the tumor were found in the urinary bladder, right ureter, pelvic, periaortic and hilar lymph nodes, pancreas and in one ganglion In addition, there was a right hydroureter above the level of the tumor, chronic fibrous perisplenitis and hemosiderosis of the spleen and liver

SUMMARY

The developmental anatomy of mesonephric tissue has been reviewed and its anomalous locations and resulting circumstances cited

All previous clinical reports of mesonephromata have been reviewed and cited

A case report of mesonephroma of the right ovary with invasion of the bladder wall is presented

It is our belief that this is the first report of such a situation

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FACTORS IN THE PROGNOSIS OF CARCINOMA OF THE KIDNEY

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While the urologist is naturally most interested in diagnosis and treatment it is also important for him to have a knowledge of prognosis, even if only to explain to the relatives the likely outcome of his successful operation. In adenocarcinoma of the renal parenchyma, to which my remarks will be confined, there is general agreement, in the different series which have been reported, on the average survival rate after a stated period. Thus in 395 cases reported by Priestley (1939), in 103 cases reported by Griffiths and Thackray (1949) and in 685 cases of the British Association of Urological Surgeons series (Riches, Griffiths and Thackray 1951) it was found that about 50 per cent of patients survived for 3 years, about 40 per cent for 5 years and about 20 per cent for 10 years. The prognosis in the individual case, however, varies widely and while one may die early, another may live for 20 years or more, even if untreated the average 3-year survival rate is about 3 per cent. While there can be no mathematical accuracy in such a matter it is possible after a complete study of all the factors concerned to give a prognosis which is at any rate more accurate than a racing forecast. These factors are 1) the histological grade of the tumor, 2) involvement of the renal vein, 3) invasion of lymph nodes, 4) local extension of the growth, 5) presence of metastases and 6) the method of treatment.

In an attempt to assess the relative value of each of these factors I have been through the records of 84 personal cases. Eight (10 per cent) were inoperable leaving 76 in which all the factors were known after operation. The operative mortality was six (8 per cent). Although 25 of the patients were living from 5 to 10 or more years after operation I have limited my report to those surviving for 5 years in order to have a reasonable number on which to base conclusions. Of the 76 patients, 54 were operated upon five or more years ago, and these form the basis of the survival tables.

HISTOLOGICAL GRADE

The grading is based solely on the microscopic appearance of the tumor. Of the two common types of well differentiated carcinoma the tubular adenocarcinoma is usually composed of clear cells and has well marked tubules resembling those of the kidney, the papillary cystic adenocarcinoma shows cystic spaces full of branching papillary processes its cells are often granular, but any one tumor may contain both clear and granular cells in different areas and the type of cell appears to bear no relation to the malignancy. Both of these tumors would be classed as grade 1 if they are well differentiated. If the tubules or papillary processes are not well formed, or the cells are moderately irregular and show some mitotic activity, the tumor will be placed in grade 2. If there is no attempt at the formation of tubules or papillary processes, but marked varia-

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Read at annual meeting of the American Association of Genito-Urinary Surgeons, Hot Springs, Va., May 1–3, 1957.

TABLE 1 *April 1957*

Total 84 Inoperable 8 (10%)

Nephrectomy	76
Grade 1	37
Grade 2	24
Grade 3	15

Operative mortality 6 (8%)

TABLE 2 *5 year survival, April 1957*

	Possible	Actual
Total	54	27 (50%)
Grade 1	24	17 (71%)
Grade 2	18	7 (39%)
Grade 3	12	3 (25%)

tion in the size and staining of the cells and their nuclei, with considerable mitotic activity, it falls into grade 3 It is obvious that the grading must be done by a skilled pathologist accustomed to this work and I have been fortunate in having the help of Dr A C Thackray for this purpose Neither the size of the tumor nor its gross appearance gives any real clue to the histological grade

Table 1 shows the number of tumors in each grade in this series

Table 2 shows the number of those who survived for 5 years The rising scale of histological malignancy is reflected in a falling survival rate Although some of these figures are too small to be expressed as percentages, they correspond closely with the figures we reported in the previous series, although we now have one 10-year survivor in grade 2 and two in grade 3

INVOLVEMENT OF THE RENAL VEIN

It is well known that these tumors invade the radicals of the renal vein early and extend into its main trunk and thence to the vena cava Involvement of the vein is here intended to mean macroscopic invasion of the main trunk or its tributaries It occurred in 30 per cent of the operable cases in this series

In table 3 it will be seen that venous involvement was less common in the low grade tumors than in those of the higher grades of malignancy, and there is an undoubted correlation between the two factors

TABLE 3 *Involvement of renal vein*

	No	Vein Invaded
Total	76	22 (30%)
Grade 1	37	5 (13%)
Grade 2	24	11 (46%)
Grade 3	15	6 (40%)

TABLE 4 *5-year survival Vein involved*

Total	4 out of 16 (25%)
Grade 1	1 out of 3
Grade 2	2 out of 7
Grade 3	1 out of 6

One quarter of the possible 5-year survivors with the vein involved did actually live for this period, but the figures are too small to justify any conclusions If the whole series is examined however, we find that out of the 22 with venous involvement no less than 14 (64 per cent) died ultimately from metastases, and if the three operative deaths in this group are excluded the percentage dying from metastases rises to 14 out of 19 or 74 per cent It is thus evident that venous involvement has a very sinister effect on prognosis From the practical point of view it is important to try and divide the renal vein beyond any palpable growth, and it is sometimes worthwhile to open the vena cava and extract any tumor embolus within reach One patient in whom this was done returned to work and lived for over 4 years before dying of a recurrence

INVASION OF LYMPH NODES

Palpable invasion of lymph nodes occurred in six patients in this series, of whom two survived for five years Lymphatic invasion does not appear to have any connection with the grade of the tumor as it occurred in 8 per cent of each of grades 1 and 2 and 7 per cent of grade 3 It is an indication for postoperative x-ray therapy, and we have found that the response to treatment is generally good Eventually however, in five of the six cases metastases developed A man of 62, with a grade 1 tumor, from whom invaded glands adherent to the vena cava were removed, lived for four years before dying of recurrence in the lung A woman of 37, with a grade 2 tumor, had a mass of glands adherent to the aorta which I could not remove, they disappeared under x-ray treatment but recurred in the neck and disappeared again with treatment They recurred here again and I excised them She remained well for nearly six years before dying from multiple metastases Another patient, whose glands were removed at the time of operation, lived for 7½ years before dying from carcinoma of the stomach Although lymphatic invasion is an important factor in prognosis it does not appear to have such an early lethal effect as a high grade of tumor, but locally invaded lymphatics should always be removed with the kidney if possible

LOCAL EXTENSION

By local infiltration the tumor may invade the perinephric fat, the surrounding muscles, the colon, the pancreas or other viscera (table 5)

It occurred in 24 per cent of the whole series and was more evident in the higher grades of tumor Its effect on survival cannot always be anticipated but it is an obvious indication for x-ray treatment either before or after operation If there is clinical evidence of local fixity it is worthwhile confirming this by perirenal oxygen insufflation, and preoperative x-ray therapy will sometimes

TABLE 5 *Local extension*

	No	Present	5-Year Survival
Total	76	18 (24%)	5 out of 9
Grade 1	37	5 (13%)	2 out of 3
Grade 2	24	7 (29%)	2 out of 2
Grade 3	15	6 (40%)	1 out of 4

TABLE 6 *Metastases present at operation*

		Present
Total	76	7 (9%)
Grade 1	37	3 (8%) Bones 3
Grade 2	24	3 (13%) Lungs 2, bones 1
Grade 3	15	1 (7%) Liver 1

Longest survivor living and well at 4 years

make a fixed tumor operable One such patient, with a grade 2 tumor and the vein involved, is alive and well five years after operation Another a man of 47, was explored elsewhere and found to have a fixed inoperable renal tumor He took a course of x-ray treatment and the tumor became smaller I then re-explored, divided some adhesions and removed the kidney He remains well more than 10 years later although it was a grade 2 tumor with the vein involved

METASTASES

Even in the presence of known metastases it is sometimes advisable to perform nephrectomy, either to relieve pain or hematuria, to control pyrexia or on the assumption that x-ray treatment of a secondary deposit will be more effective if the primary growth has been removed See table 6

In only one of these patients have I found it possible to remove the metastasis after removing the kidney This man of 65 had a grade 1 tumor with the vein free, five weeks after doing the nephrectomy I removed part of his chest wall which showed a similar growth in the seventh rib, he remains well four years later It is well known that in this disease the metastasis is sometimes solitary, the possibility of its removal should always be borne in mind The preoperative detection of a metastasis in the liver was made in one case by aortography, it showed not only an area of pooling in the kidney but another in the liver, fed by a branch of the hepatic artery, it was palpated at the time of left nephrectomy but unfortunately appeared too large for successful extirpation

METHOD OF TREATMENT

Some of the possibilities of preoperative x-ray treatment have already been mentioned and it is open to question whether the results in general could not be improved by a more extensive application of this form of therapy Regarding postoperative x-ray treatment we found, in the analysis of the larger series of cases previously reported (1951), that the survival rate was increased in those

TABLE 7 *Incidental finding of carcinoma*

	No	Nephrectomy for	Survived 5 Years
Grade 1	4	Calculi	3
Grade 2	2	1 hydronephrosis, 1 hypertension	1 1
Grade 3	1	Suspected calculus	0
Total	7		5

patients who had received postoperative treatment Moreover, the increase was most marked in those tumors, generally of high grade malignancy, in which the vein was involved There are often cogent reasons for not giving x-ray treatment to a particular patient, but I believe that it should be given in all tumors of high grade, in those where the vein is involved, where lymph nodes are invaded or where there is evidence of local extension

The surgical treatment should be radical and should include the removal of the perinephric fat, invaded glands and, if necessary, other viscera Exposure must be adequate, and the approach used is usually through the bed of the excised twelfth rib Occasionally the Nagamatsu incision is used and in a few instances the abdominothoracic approach

When all is said however, we must realize that the key to successful results is early diagnosis With the aid of aortography we have been able to diagnose the presence of a tumor less than one inch in diameter There have also been 7 patients in whom the finding of a new growth was accidental, the kidney being removed for some other reason (table 7)

Five of the seven have lived for more than 5 years A grade 1 patient died from pulmonary embolism, and a grade 3 patient whose kidney contained the smallest tumor I have ever removed was back in less than 2 years with extensive metastases

The longest survivor in the whole series, a woman of 48, is alive and well more than twenty years after operation It was a grade 1 tumor with the vein free, and it was enclosed in a calcified shell

There must be an exception to prove every rule, in this series it is provided by a man of 60 who was investigated for loss of weight and was found to have a grade 3 tumor with the vein invaded and extension of growth into the perinephric fat He is alive and well more than 8 years after operation

SUMMARY

The factors influencing the prognosis in carcinoma of renal parenchyma have been considered in a series of 84 cases, of which 76 were treated by nephrectomy

The histological grade of the tumor is the most important factor, and involvement of the renal vein has a serious adverse influence

Surgical excision must be radical and early to have a chance of permanent success

X-ray therapy either before or after operation has a place in treatment and increases the survival rate

The probable outcome of an individual case can be foretold with reasonable accuracy when all the factors are known

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MALIGNANT NEOPLASMS OF THE KIDNEY AN ANALYSIS OF 353 PATIENTS FOLLOWED FIVE YEARS OR MORE

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It is the purpose of this report to present an analysis of 353 patients with malignant neoplasms of the kidney confirmed by microscopic tissue study and followed for five years or more by the Tumor Clinic at the University Hospitals in Iowa City, Iowa These patients were seen during the period 1926–1950, inclusive These tumors were classified as follows

Renal cell carcinoma	305
Embryoma (Wilms' tumor)	31
Tumors arising from renal pelvis (epidermoid and transitional cell carcinomas)	17

They were staged on the basis of the extent of the primary lesion as follows

Stage 1—Limited to the renal capsule
Stage 2—Invasion of the renal pedicle and/or renal fat
Stage 3—Regional lymph node involvement
Stage 4—Distant metastasis demonstrable

Two hundred and forty-three of these patients were seen prior to 1946 and thus enabled us to obtain the results of a 10-year or more followup study These were classified as 220 renal carcinomas, 22 embryomas, and 11 tumors of the renal pelvis

RENAL CARCINOMA

Three hundred and five cases of renal carcinoma were analyzed One hundred and sixteen of these were in stage 4 and 21 cases were not staged Fifty-two received only palliative treatment due to advanced age or general debility and these were not considered as treated cases Of the 137 treated cases, four were of unknown stages but were included in all the studies except those related to stage of the disease Tables 1 to 5 summarize the results of these analyses Treatment, when used alone in these tables, means an attempt to destroy the tumor by nephrectomy, irradiation, or a combination of nephrectomy and irradiation

Table 1 gives the five- and 10-year survival according to the stage at the time of the diagnosis and compares the treated cases with the over-all group in the various stages Twenty-one cases were not staged and therefore are not included in this table

It is to be noted that the five- and 10-year survival is very definitely improved by the institution of therapy in all stages studied In stage 1, 16 patients received no therapy Of these only two survived, making a five-year survival of 12½ per cent as contrasted to 55 per cent in the treated cases Similarly, of the 10-year cases one of 14 survived, making a 7 per cent 10-year survival as contrasted

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Read at annual meeting of the American Association of Genito Urinary Surgeons Hot Springs Va , May 1–3, 1957

TABLE 1 *Renal carcinoma*

	Followup	Number of Cases	5 Year Survival	10-Year Survival
Stage 1, over all	5 year	76	35 (46%)	
	10 year	58	23 (40%)	11 (19%)
Treated cases	5 year	60	33 (55%)	
	10 year	44	22 (50%)	10 (23%)
Stage 2 over all	5 year	59	22 (37%)	
	10 year	47	18 (38%)	12 (28%)
Treated cases	5 year	52	21 (40 5%)	
	10 year	42	17 (40 5%)	11 (25 5%)
Stage 3, over all	5 year	33	3 (9%)	
	10 year	21	2 (9 5%)	2 (9 5%)
Treated cases	5 year	21	3 (14%)	
	10 year	12	2 (16 6%)	2 (16 6%)
Stage 4	5 year	116	4 (3 5%)	
	10 year	79	3 (3 8%)	1 (1 3%)

TABLE 2 *Renal carcinoma*

	Followup	Number of Cases	5 Year Survival	10-Year Survival
Total cases	5 year	305	71 (23%)	
	10 year	220	48 (22%)	27 (12 3%)
Treated cases*	5 year	137	41 1%	
	10 year	101	40 6%	22 8%
Treated by nephrectomy*	5 year	56	48 2%	
	10 year	39	46%	23%
Treated by x ray plus neph *	5 year	40	52 5%	
	10 year	27	55%	33 3%
Treated by x ray only*	5 year	41	24 4%	
	10 year	35	23%	14 5%
No treatment*	5 year	50	10%	
	10 year	40	12 5%	5%
Treated by x ray pre-op then neph	5 year	25	(13) 52%	
	10 year	14	(8) 57%	(7) 50%

* Cases in stages 1, 2 and 3

with a 23 per cent survival in the treated cases For stage 2 cases a similar analysis shows a 14 per cent five-year survival for the untreated as contrasted to a 40 per cent survival for the treated, and, similarly, a 20 per cent 10-year survival as contrasted to a 25 per cent survival in the treated cases In stage 3 the contrast is even more marked There is a zero per cent survival in the untreated cases as contrasted to a 14 per cent five-year, and 16 per cent 10-year survival These figures would seem to indicate that in those patients where therapy was utilized the prognosis was better either because of the intrinsic nature of the situation or because of the therapy itself Moreover, it would seem that there is little difference between stages 1 and 2 as far as prognosis is concerned, but the results in stages 3 and 4 were definitely worse

Table 2 illustrates the effects of the various types of therapy upon survival

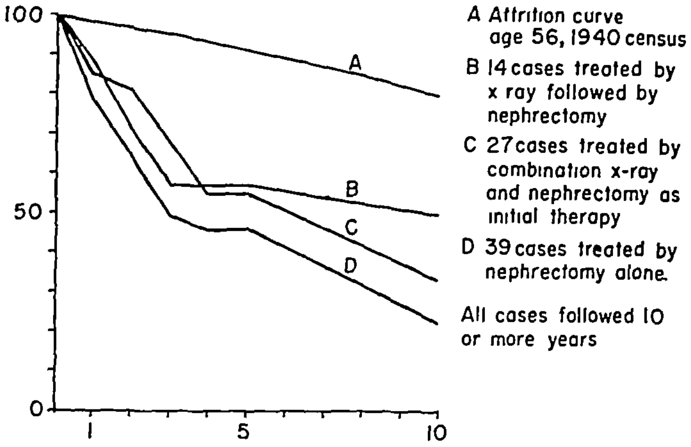

FIG 1

It demonstrates again the marked improvement in survival in the treated cases as contrasted to the untreated cases It is of interest also to note that the combination of nephrectomy and irradiation produces what seems to be significantly better results than nephrectomy alone The total number of cases is small but the difference particularly in the 10-year survival group is so marked that it may be of real significance Figure 1 illustrates the difference between nephrectomy alone and the combined treatment cases as far as 10-year survival is concerned It shows that those of the combined treatment group who have passed the five-year mark have a mortality which is no greater than that of the general population It is also of interest to point out that the only two patients in stage 3 who survived 10 years and the one case in stage 4 that did so received irradiation as part of their therapy Table 3 shows an analysis of survival related to staging in the 25 patients who received preoperative irradiation followed by nephrectomy We want to emphasize the 10-year survival figures in this group These patients all received approximately 7000 roentgens through several ports over a period of three weeks Six weeks later nephrectomy was carried out Irradiation therapy seemed to have shrunk some of the dilated veins and made the nephrectomy in no way more difficult Aside from shrinkage of collateral

TABLE 3 *Renal carcinoma*

Treated by X Ray Pre-op followed by Nephrectomy	Followup	Number of Cases	5 Year Survival	10-Year Survival
Stage 1	5 year	9	6 (66 6%)	
	10 year	5	2 (40%)	2 (40%)
Stage 2	5 year	12	7 (58%)	
	10 year	8	6 (75%)	5 (62 5%)
Stage 3	5 year	3	0 (00%)	
	10 year	1	0 (00%)	0 (00%)
Unknown stage	5 year	1	0 (00%)	
	10 year	0		

TABLE 4 *Renal carcinoma*

Author Date	Followup	Number of Treated Cases	5 Year Survival	10-Year Survival
Bergendal, 1936	5 year	57	40.4%	
	10 year	40		30%
Beer, 1937	5 year	?	Apparent 34%	
Priestley, 1939	5 year	357	38.4%	
	10 year	253		27.3%
Melicow, 1943	5 year	20	50%	
Bixler, et al., 1944	5 year	64	35.5%	
Foot, et al., 1949	5 year	37	41%	
	10 year	17		23%
Dick and Flint, 1951	5 year	36	46%	
Throckmorton, 1955	5 year	22	36.3%	
	10 year	14		14.5%
Goldstein, 1956	5 year	77	31%	
This series, 1957	5 year	137	41.1%	
	10 year	101	40.6%	22.8%

TABLE 5 *Renal carcinoma*

Duration of Symptoms	5-Year Survival	
	Over all	Treated cases
Less than 1 month	31%	60%
1–6 months	16%	24%
7–12 months	12%	16%
1–2 years	11%	27%
2–3 years	35%	43%
3–5 years	31%	50%
5–10 years	56%	64%
Over 10 years	20%	20%

circulation no other unusual gross or microscopic changes in the tumor were noted in these patients at the time of operation.

It is of interest moreover to compare tables 1, 2, and 3 with table 4. Table 4 is a summary and comparison of five- and 10-year survivals of patients with renal carcinoma as reported in the literature by various investigators of the past 20 years. It would seem that the over-all results with the exception of the small group receiving combined therapy have been essentially the same at various times and in various hands.

Table 5 gives the percentage survival according to the duration of symptoms prior to institution of symptoms. These figures were analyzed to obtain further information with regard to the life history of this tumor. Their significance is not clear. They are simply presented for the record.

EMBRYOMA (WILMS' TUMOR)

There were 31 embryomas of the kidney in this series. All but three received treatment. Table 6 summarizes the results in our series and compares these with

TABLE 6 *Wilms' tumor*

Author Date	Followup Period	Number of Cases	2 Year Survival	5 Year Survival	10-Year Survival
Priestley,* 1939	3-year	17	4(23 5%)	3 (23 5%)	
	5-year	15			
	10 year	11			1 (9 1%)
Ladd, 1941		60	14 (23%)		
Weisel, 1943		44	7 (16%)		
Nesbit, 1946		16	8 (50%)		
Foot et al , 1949	5-year	11		3 (27%)	
Gross and Neuhauser, 1950		38	47 3%		
Haines, 1954		18	7 (38 8%)		
This series					
Treated by x ray only	5-year	14	4 (28 6%)	2 (14 3%)	
	10 year	10	2 (20%)	2 (20%)	0 (00%)
Treated by x ray pre-p plus nephrectomy	5 year	14	7 (50%)	5 (35 7%)	
	10 year	9	5 (55 5%)	4 (44 4%)	2 (22 2%)
Over all	5 year	31	11 (35 5%)	7 (22 6%)	
	10 year	22	7 (32 5%)	6 (27 3%)	2 (9 1%)

* Treated cases

† All but 2 treated with surgery plus post op irradiation

TABLE 7 *Tumors of the renal pelvis*

Author Date	Followup	Number of Treated Cases	5 Year Survival	10 Year Survival
Priestley, 1939	5-year	40	14 (35%)	
	10-year	19		2 (10 5%)
Foot, et al , 1949	5 year	12	3 (25%)	
Dick and Flint, 1951	5-year	8	2 (25%)	
This series	5 year	17	7 (41%)	
Over all	10 year	11	3 (27 2%)	1 (9 1%)
Treated cases	5 year	11	5 (45%)	
	10 year	6	2 (33%)	1 (16 5%)

others reported in the literature It is to be noted that our two-year survival in the 14 cases treated by preoperative irradiation followed by nephrectomy is similar to the two-year survival in a larger group of patients reported by Gross and Neuhauser It is also to be noted that 2-year survival is by no means indicative of a cure There is every indication from the study of this group of cases and from the reports in the literature such as that of Gross and Neuhauser that irradiation is an important part of the therapy of these cases Preoperative x-ray treatment proved useful in this group of patients

TUMORS OF THE RENAL PELVIS

There were 17 tumors of the renal pelvis and the results of an analysis of these cases are compared with some similar groups reported in the literature in table 7 Note that only one patient lived and is living 10 years after the institution of therapy which consisted of nephro-ureterectomy No combined therapy was instituted in this group of patients Whether it would alter the poor prognosis is not known and deserves study

SUMMARY

An analysis of 353 cases of malignant renal neoplasms studied at the University Hospitals from 1926 to 1950, inclusive, is presented

With regard to renal carcinoma, combined surgical and radiation therapy seems to have given better results than simple surgery alone Further studies are needed in this regard

A small group of Wilms' tumors is analyzed From this study it would seem that 2-year survival does not necessarily mean a cure of this dread disease Moreover, combined therapy is superior to either irradiation alone or surgery alone

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ACUTE REGIONAL URETERITIS

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In 1910 Hunner first brought forth his concepts of ureteral inflammation and stricture This subject was discussed considerably in the urological literature up into the late twenties In MODERN UROLOGY, edited by Cabot, Randall and Campbell (vol 2) write "Urology owes Hunner a debt of thanks for his extreme interest in this subject of ureteral stricture and his pertinacity in making everyone cognizant of the possibility of the part that ureteral stricture may be playing in every case of apparent obstructive uropathy With the enthusiasm of the propagandist it is not to be wondered at that Hunner carried his ideas further than the rank and file were willing to follow Nor is it strange that in his efforts to hammer home his subject, cause and effect occasionally became confused "

In Hunner's opinion, the majority of strictures have origin in an infection of the ureteral walls from some distant focus He called this ureteral inflammation "primary" and other urinary tract lesions as stone, hydronephrosis, pyelonephritis, etc , which occurred were secondary to the stricture which followed the inflammation

Legueu and Fey differed with Hunner and stated that "neither clinical examinations nor the results of treatment nor the anatomical manifestations have given us the proof which we demand We believe we can justly conclude that nothing permits to attribute to a stricture the troubles which are called Hunner's syndrome " In this great controvery which is now urological history there was much discussion about clinical observations, technique of treatment, about the "hang of the wax-bulb", etc When pyelograms were taken there was doubt as to their proper interpretation Even then W F Braasch remarked that ureteral spasm explains many cases of so called ureteral stricture diagnosed by means of ureteral bulbs It is interesting to note that F C Herrick suggested gravity pyelograms

Most scanty of all are the attempts to prove by pathological and histological examination, the nature of what was supposed to exist In a paper by Braasch and Hurley, localized areas of hyperplasia of the mucosa and submucosa resulting from inflammation are described as relatively frequent findings in the entire urinary tract They called these areas "granulomas " These varied from minute patches to papillomatous proliferations most frequently found in the bladder and urethra but also in the whole urinary tract These can cause hematuria, persistent infection and may be confused with neoplasm, particularly when close to the ureterovesical junction The possibility of stone has to be excluded The authors report a case where a patchy filling defect in the lower left ureter suggested tumor In spite of negative biopsy, a uretero-nephrectomy for neoplasm was done Examination revealed only a localized hemorrhagic inflammatory and edematous condition of the lower one-third of the left ureter We recently ob-

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served two cases which may contribute some knowledge to the problem of ureteral stricture

CASE REPORTS

Case 1 Mr G B, aged 63, born in Italy, was admitted on January 3, 1953 complaining of colicky, sudden pain in left flank of three days' duration He gave a history of a previous similar attack lasting two days, but he never passed a stone At that time an intravenous pyelogram was negative The pain radiated anteriorly into the penis and there was nausea, urgency, and frequency The physical examination was negative except for costovertebral tenderness on the left side and no masses were felt The blood pressure was 124/78, temperature 37 4 The blood count was normal The urinalysis was negative, except for a moderate number of white and red blood cells The blood chemistry determinations were within normal limits, except that the uric acid was 7 25 mg per cent and the urine uric acid 86 mg per cent Bacteriological examination of urine from the left kidney was negative An intravenous pyelogram on January 14 showed that the renal and psoas shadows were within normal limits in size and position Some calcification was present in the pelvic vessels No shadows were identifiable as calculi The dye was present in both kidneys five minutes after injection The internal structure of the right kidney and ureter appeared to be within normal limits There was some dilatation of the left renal calyces The entire left ureter was visualized to the region just above the pelvic portion and this ureter was slightly dilated as compared to the right one (fig 1, *A*) There was

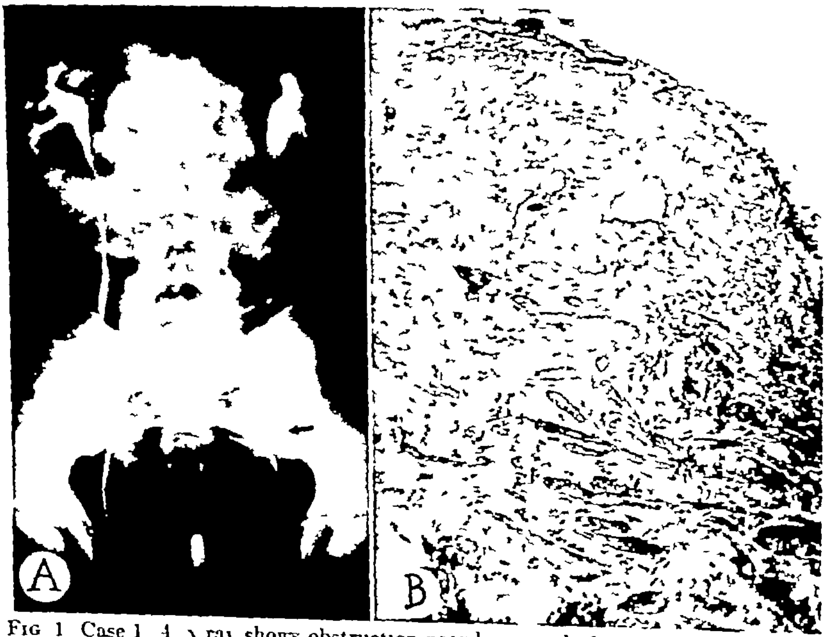

FIG 1 Case 1 *A* X ray shows obstruction near lower end of ureter *B* granulomatous ureteritis with suggestive ulceration

fairly good concentration of the dye in the bladder at the end of 60 minutes and some suggestion of elevation of the floor of the bladder The x-ray interpretation was an indication of obstructing lesion of the lower end of the left ureter most likely a calculus, although a calculus was not identified A cystoscopic examination was performed on January 14 The urine obtained from the bladder was yellow with a large number of shreds There was moderate trilobar prostatic hypertrophy Except for mild trabeculation, the bladder including the orifices appeared normal Indigo carmine appeared in 3 minutes and in good concentration on the right side The left side showed no function for 20 minutes and then observation was discontinued A size 5 ureteral catheter was easily inserted on the right side The secretion was clear On the left side the catheter was accepted for 15 cm at which point there was a definite obstruction The flat film disclosed a filling of the left kidney pelvis and ureter from the intravenous pyelogram taken the day before The filling went exactly to the point where the tip of the ureteral catheter appeared obstructed A right retrograde pyelogram appeared normal On the left side, no dye passed beyond the tip of the ureteral catheter The diagnosis was a non-opaque calculus or tumor of the left ureter The pain and vomiting continued with evidence of a paralytic reflex ileus necessitating the passage of a Levine tube Surgery was performed three days later with a preoperative diagnosis of "non-opaque calculus, stricture, tumor, or tuberculosis of the left ureter "

Under spinal anesthesia, a cystoscopy was done and the left ureter was again catheterized A No 5 catheter stopped at 15 cm The patient was then placed in a right oblique position with the left side slightly elevated An incision was made along the course of the ureter beginning about 5 cm below the iliac spine and extended as much upward toward the tip of the last rib The ureter was approached retroperitoneally and its midportion exposed The ureteral catheter was felt Above it there was an area of infiltration of the wall of the ureter extending 4 to 5 cm in length upward, and beyond this it appeared normal in consistency and caliber The ureter was palpated to the kidney pelvis without abnormality noted The same was true below the obstruction towards the bladder The infiltrated portion of the ureter was shelled out with relative ease from the surrounding tissue It was opened and the wall was found to be definitely thickened and edematous with some edema of the surrounding tissue in this area The mucous membrane lining of the ureter appeared normal After the infiltrated portion of the wall was slit the whole length, there was no difficulty in inserting the size 5 catheter downwards to the bladder as well as upwards to the kidney Slightly blood tinged urine drained in continuous drip At this point, a biopsy was taken from the wall at three different sites The pathologist's diagnosis was "inflammatory, non-specific, and not malignant tissue " It was not considered justifiable to sacrifice the kidney and, therefore, a T tube was inserted upward toward the kidney and downwards toward the bladder Before this was done, a No 12 bougie was inserted in the lower part of the ureter to the bladder The free end of the T tube was conducted out through the lateral stab wound in the abdominal wall The ureter was then placed in its bed and a Penrose drain was placed at the lower end of the wound, which was closed in layers The patient went through the procedure in good condition

Pathological report The gross specimen consisted of three portions of material from the ureter, largest 5 mm in length, grayish pink The second specimen was firm, grayish brown and soft The third measured 3 mm in diameter

Microscopic description Sections showed a portion of ureter with an occasional lining of transitional epithelium recognizable In the underlying wall, there was evidence of thickening due to hyperemia with non-specific granulation tissue formation consisting of loose strands of collagen and fibroblasts with marked edema between There were some areas showing dilatation of veins In one area, there was some crystallin-like material suggesting portion of a stone in a nest of smooth muscle The diagnosis was "chronic ureteritis, non-specific, probably due to lithiasis with mucosal ulceration " See figure 1, *B*

The patient improved rapidly and drained approximately 500 to 600 ml of urine in 24 hours through the T tube This gradually diminished and the vesical output increased On the third postoperative day, he suffered a typical gouty attack in his right big toe He was placed upon a purine free diet and colchicine The blood uric acid level responded slowly although there was a rapid clinical response The uric acid dropped to 3 5 mg X-rays of both hands January 30 showed evidence suggesting a gouty arthritis On February 7 the T tube was removed The wound closed rapidly and he was discharged February 12 in good condition He was advised to continue the diet and the urine was alkalinized with citrocarbonate Instead of increasing the uric acid output, we would rather try to dissolve the uric acid in the urine and in this manner prevent complications of uraturia Approximately 4 years later, the patient has had no recurrence of either his gouty attacks or of any renal disturbance

Case 2 Mr W B aged 60, was admitted October 22 complaining of painless hematuria of one day's duration One week before hospitalization he noted moderate low back pain The urine was bright red throughout urination, no clots were present Examination showed a well built well preserved man The physical examination was negative except for some tenderness in the upper area of the lumbodorsal joint more on the left than right Blood pressure 160/100 temperature 37 degrees The urinalysis shows specific gravity of 1 006, yellow, clear acid, albumin negative, sugar negative, microscopic examination was positive for white cells and red cells Urine culture was negative Alkaline and acid phosphatase determinations were normal Several uric acid determinations varied from 3 9 to 4 1 mg per cent Sedimentation rate was 7 mm in 60 minutes which rose to 24 mm in 60 minutes within a week The remainder of the blood chemistry was within normal limits and the blood count was within normal limits Intravenous pyelography performed on October 25 showed normal appearing kidney shadows bilaterally without renal stone shadows Both kidneys excreted normally There was slight relative dilatation of the left collecting system left renal pelvis, and upper two-thirds of the left ureter, but this was not a consistent feature in all of the films The bladder shadow was normal with a slight increase in trabecular pattern and there were prostatic calculi The conclusion at this time was "essentially negative intravenous pyelogram with prostatic calcification"

Cystoscopy was performed October 24 The urethra appeared normal There was slight intrusion of the posterior urethra and the lateral lobes of the prostate gland and mild bar formation The surface of the bladder including the orifices was entirely normal A size 5 ureteral catheter was easily inserted on the right side On the left side neither a size 5 nor 4 catheter was accepted beyond 10 cm The right pyelogram was normal On the left it was impossible to obtain filling beyond the spot marked by the tip of the catheter 10 cm above the bladder A gravity pyelogram using a Braasch bulb catheter No 10 did not succeed beyond 10 cm There was definitely an obstruction at this point The patient subsequently continued to complain of pain at the level of the left sacroiliac joint Intravenous pyelography was repeated on October 26 The right upper urinary tract appeared normal and there was no evidence of obstruction or dilatation of the right ureter In comparison with previous examinations 3 days ago, there appeared to be a change in that the pelviectasis and caliectasis on the left side had become more marked with evidence of a further dilatation of the left ureter The ureter was well seen and was dilated to the inferior aspect of the left sacroiliac joint (fig 2, *A*) There was no definite calcification within the ureter The bladder was not changed The conclusion at this time was that apparent further obstruction in the left upper urinary tract had occurred in the past three days with the point of obstruction being near the inferior aspect of the left sacroiliac joint A calculus could not be identified The intravenous pyelogram was repeated October 30 The conclusion at that time was "persistent left hydronephrosis and left hydro-

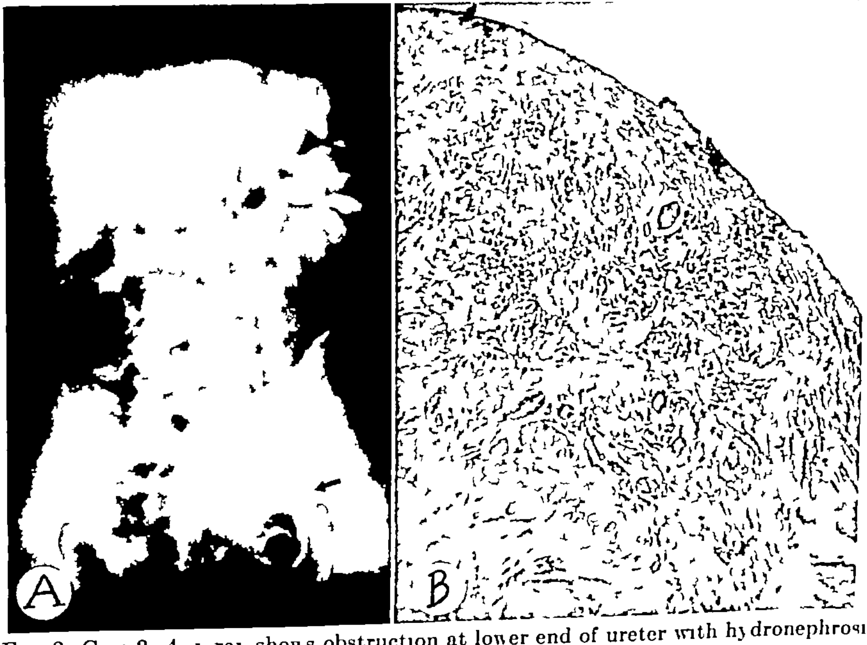

FIG 2 Case 2 *A*, x ray shows obstruction at lower end of ureter with hydronephrosis *B*, granulomatous ureteritis with foreign body reaction

ureter without change " It was decided to explore the ureter with a tentative diagnosis of ' tumor, non-opaque stone, or ureteritis "

The operation was performed November 1 A Foley catheter was inserted and kept under constant drainage A lower hockey stick incision was made beginning above the os pubis along the left border of the rectus muscle upward to the level of the umbilicus The incision was carried retroperitoneally and the ureter identified where it crossed the iliac vessels The ureter appeared undisturbed except for an area approximately 1 cm below the crossing and here there was infiltration of the wall and thickening Above and below this area it appeared normal in size and the wall felt normal The caliber of the lumen above was somewhat wider than below The ureter was grasped between Babcock forceps and adhesions in that area were severed Several small vessels had to be ligated The ureter was opened and no stones were found The wall appeared edematous, thickened and apparently infiltrated for a length of 2 to 2½ cm A small portion of wall was resected and a frozen section examination was performed The diagnosis was inflammatory and granulomatous tissue " The ureter was slit and splinted in this whole area A small opening was made approximately 2 cm above the uppermost point in the opening of the ureter and a T tube was conducted upward into the kidney and the other end down into the distal end of the ureter The edges of the slit ureteral area in the inflammatory section were approximated by sutures of 0000 chromic catgut in order to prevent the catheter from bulging out A Penrose drain was inserted in the operative field The long stem of the T tube was conducted out from the wound through a separate lateral stab wound The incision was then closed in layers and the T tube was secured with one separate silk suture The patient left the operating room in good condition

Pathological report The gross specimen consisted of a small mass of tissue from the ureter 4 mm in diameter

Microscopic examination disclosed a small mass of tissue from the ureter with the mucosa showing denudation of the epithelium and replacement of the epithelium by granulation tissue extending into the underlying muscle layers Here there was fibroblastic proliferation with infiltration by large mononuclear cells some lymphocytes and occasional pus cells Diagnosis Chronic inflammatory tissue from the ureter See figure 2 *B*

Convalescence was excellent The patient was discharged after 10 days with the T tube in situ He was readmitted because of an elevation of temperature The T tube was removed and the sinus cleared spontaneously The temperature became normal An intravenous pyelogram November 20 was normal There was no more evidence of hydronephrosis and both collecting systems appeared normal in appearance The conclusion at this time was return to normal as compared with the old films The patient has returned to work without complaints

DISCUSSION

There is no doubt that in both of these cases there was regional acute inflammation of the ureter which caused obstructive symptoms In both patients the ureter was surgically explored because of a possibility of a ureteral tumor or stone There was clinically visible and palpable, infiltration of an area of ureter not more than 4 cm in length Biopsies proved the lesion to be inflammatory Both lesions healed well clinically and produced fairly normal pyelograms following operative splinting of the ureter The first case had a uric acid diathesis and a crystal was actually seen in one slide We assume the crystal is uric acid and the tissue reacted to its presence in the same manner as it reacts in a gouty joint with acute inflammation In the second case we were unable to demonstrate any foreign body in the area of inflammatory reaction The patient was not suffering from gout like the first one The urine cultures were negative No bacteria were seen in the tissue There was no preceding or concomitant infection in the patient to which the ureteritis could have been secondary

This condition, as described, appears to be rare, yet these two cases prove that it does exist We believe some of the "granulomas" described by Braasch and Hurley fall in the same category The etiology in our first case appears to be mechanical infiltration and chemical irritation of the ureteral wall In the second case, no definite etiology can be found If these cases had been treated symptomatically, as patients with vague abdominal symptoms often are, it is possible that the inflamed portions of the ureter would have healed with the formation of a stenosing scar It may well be that such spontaneously healed areas of regional inflammation are the origin of some of Hunner's ureteral strictures As to the nomenclature of these lesions we feel that it should express their acute character We also want to emphasize that they are strictly regional and quite different from the generalized ureteral inflammations concomitant and secondary to infections above or below the ureter It is, therefore, proposed to call these lesions "acute regional ureteritis "

SUMMARY

Two cases are presented with acute regional inflammation of the ureter Direct operative visual, as well as microscopic description of the lesion was obtained The role of these lesions as regards Hunner's conception of ureteral stenosis is discussed A definite clarifying nomenclature for these lesions is proposed

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URETERAL POLYPS

D E COMPERE, G F BEGLEY, H E ISAACKS, T H FRAZIER
AND C B DRYDEN

A six-year-old boy with multiple ureteral polyps causing hydronephrosis (fig 1) was presented during the pyelogram conference conducted by Dr T Leon Howard at the South Central Section meeting in Mexico City, 1956 The discussion stimulated the mention of two similar cases and since only 18 true benign ureteral tumors could be found among the approximately 200 cases of primary ureteral tumors in the literature, we believe that these cases should be reported Vest has classified these benign ureteral tumors on a histological basis into two types 1) the "stroma" type in which connective tissue predominates with a normal or minimal metaplasia of the epithelium, and 2) the more common "epithelial" or papillomatous type in which there are multiple layers of transitional epithelial cells sharply delineated from the underlying connective tissue

Our three cases represent the "stroma" type of pedunculated polypoid tumors sometimes referred to in the literature as fibromas, vascular fibrous polyps, or fibromyomas

CASE REPORTS

Case 1 R D C , a six-year-old boy, had noted repeated episodes of nausea, vomiting, chills and fever with right flank pain for three and a half years Pyuria which temporarily responded to various antibiotics was associated with these episodes Physical examination revealed a well developed, anemic, undernourished male child appearing chronically ill Bilateral costovertebral tenderness was the only positive physical finding The initial urinalysis was negative The hemoglobin was 10 gm , white blood count 16,500, nonprotein nitrogen 50 mg per cent and blood urea 11 1 mg per cent Intravenous pyelograms revealed prompt excretion of the dye with bilateral hydronephroses Bilateral pyeloureterograms suggested obstructions at both ureteropelvic junctions (fig 2) Exploration of upper right ureter revealed seven polyps snugly wedged within the proximal 3 cm of this ureter (fig 3, *A*) This segment of ureter was resected and an anastomosis of the remaining ureter to the pelvis was constructed over an indwelling 10F plastic tube A 16F Foley catheter was used as a nephrostomy tube A left trocar nephrostomy was done following closure of the right flank incision Pathological examination revealed the polyps to be from 5 mm to 10 mm in length and 2 mm to 4 mm in width Each was covered by normal transitional epithelium with an edematous, poorly nucleated stroma containing few blood vessels (fig 3, *B*) Convalescence was uneventful Six weeks postoperatively an antegrade pyelogram showed dye passing readily from the kidney pelvis to the bladder The nephrostomy tube was then removed When a 24-hour urine specimen from the left kidney revealed 4 0 gm urea, it was believed that

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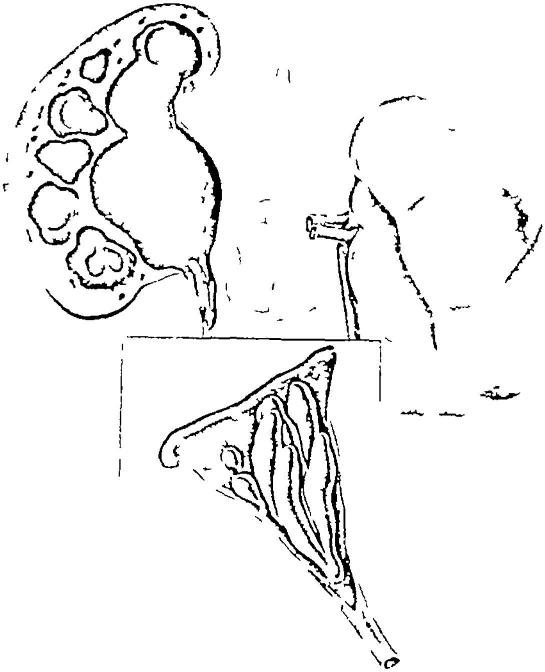

Fig 1

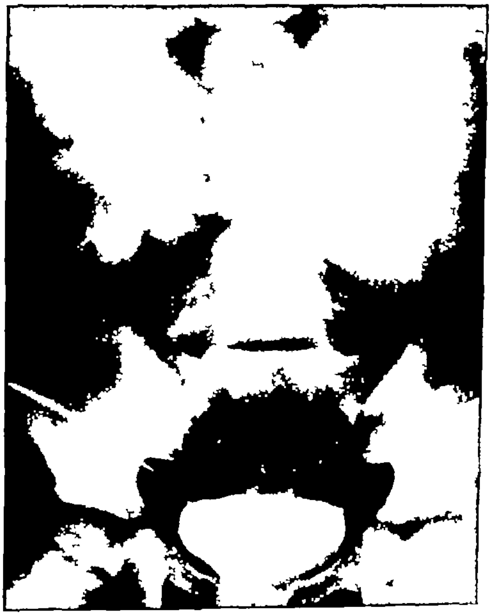

Fig 2

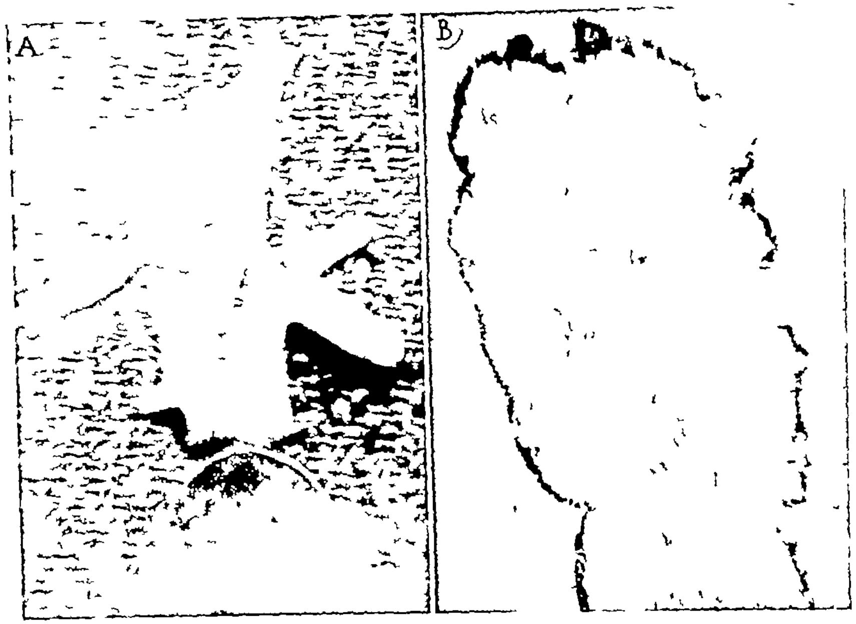

Fig 3

left pyeloplasty was justified and this procedure was done approximately two months after the initial operation An aberrant vessel was sectioned and a Foley-Schwyzer type pyeloplasty performed Convalescence was excellent and all tubes were removed in five weeks

The patient gained 15 pounds and grew two inches taller in eight months His urine became negative four months after receiving furadantin Intravenous pyelograms one year postoperatively revealed prompt excretion of the dye with slight improvement in the bilateral hydronephroses (fig 4)

Case 2 J B , a 12-year-old girl, gave a history of recurrent attacks of right upper quadrant and right flank pain associated with nausea and occasional vomiting during the preceding four years Her family physician had made a diagnosis of recurrent appendicitis, and one week prior to our seeing the patient a normal appendix had been removed by a general surgeon

Early development had been normal, and there was no history of previous genitourinary tract disease in the patient or in her family She was well developed and well nourished and the only significant physical finding was slight tenderness over the right kidney area The urine showed microscopic red blood cells and a trace of albumin The hemoglobin was 13 gm , the white blood count was 12,000 with a slight shift to the left, and the blood urea nitrogen was 14 8 mg per cent The intravenous urogram series showed prompt excretion of the opaque medium in excellent concentration bilaterally There was reduplication of the upper portion of the drainage apparatus bilaterally with all four renal segments appearing normal, except for the inferior segment on the right, which seemed to be partially obstructed at the ureteropelvic junction level, with a

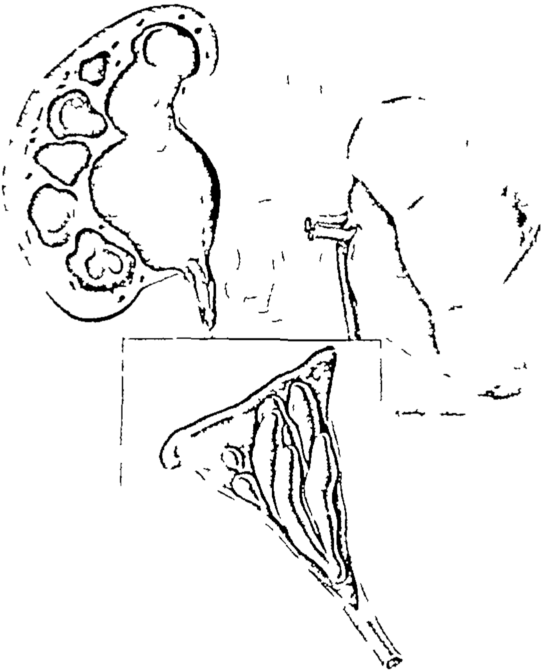

Fig 1

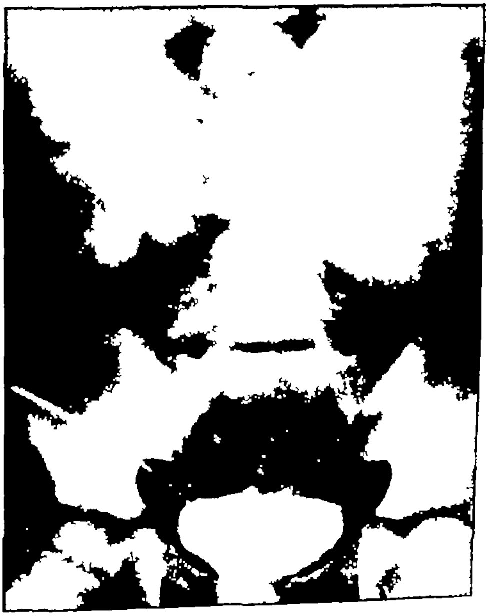

Fig 2

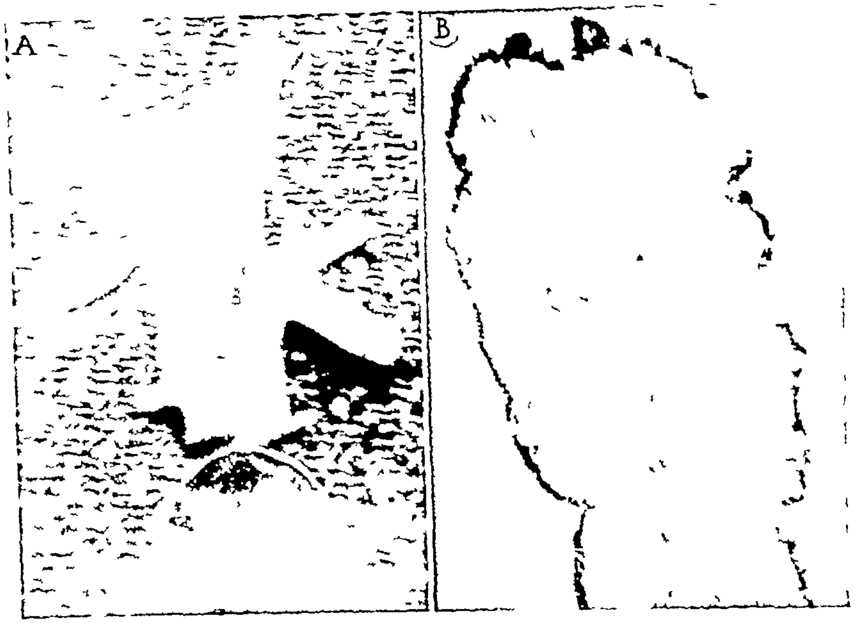

Fig. 3

left pyeloplasty was justified and this procedure was done approximately two months after the initial operation. An aberrant vessel was sectioned and a Foley-Schwyzer type pyeloplasty performed. Convalescence was excellent and all tubes were removed in five weeks.

The patient gained 15 pounds and grew two inches taller in eight months. His urine became negative four months after receiving furadantin. Intravenous pyelograms one year postoperatively revealed prompt excretion of the dye with slight improvement in the bilateral hydronephroses (fig. 4).

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Early development had been normal, and there was no history of previous genitourinary tract disease in the patient or in her family. She was well developed and well nourished and the only significant physical finding was slight tenderness over the right kidney area. The urine showed microscopic red blood cells and a trace of albumin. The hemoglobin was 13 gm., the white blood count was 12,000 with a slight shift to the left and the blood urea nitrogen was 14.8 mg. per cent. The intravenous urogram series showed prompt excretion of the opaque medium in excellent concentration bilaterally. There was reduplication of the upper portion of the drainage apparatus bilaterally with all four renal segments appearing normal, except for the inferior segment on the right which seemed to be partially obstructed at the ureteropelvic junction level with a

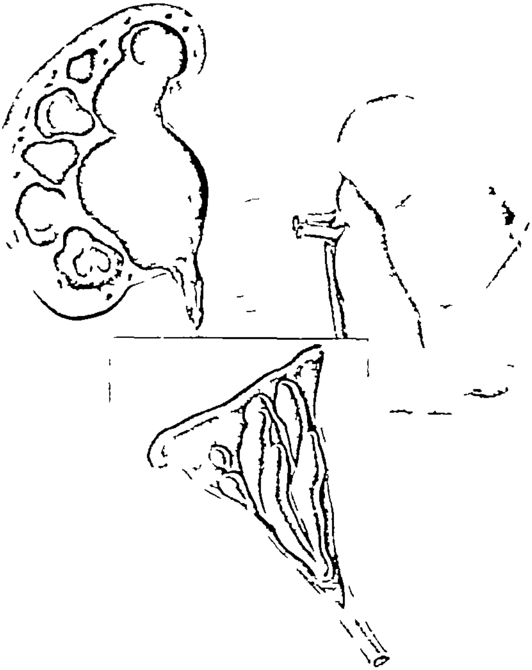

FIG 1

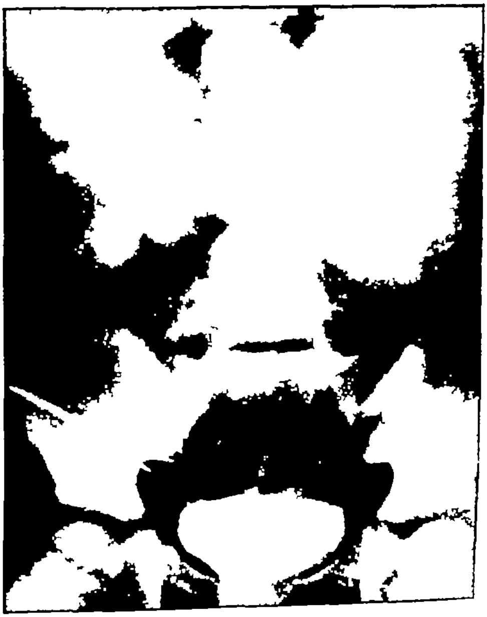

FIG 2

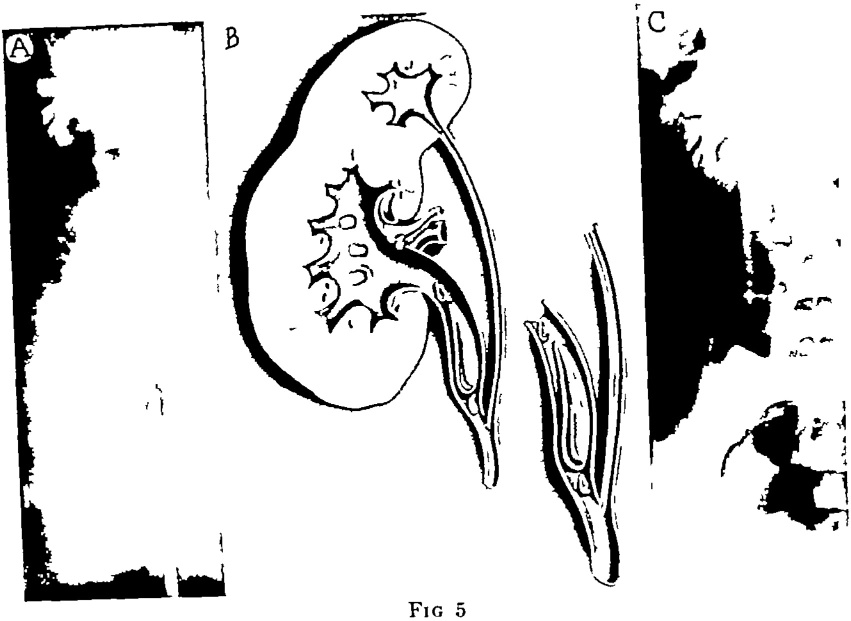

FIG 5

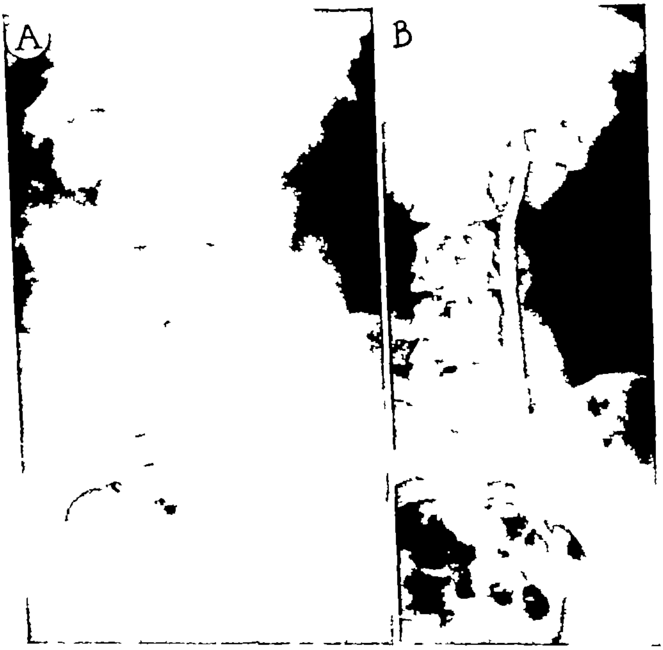

FIG 6

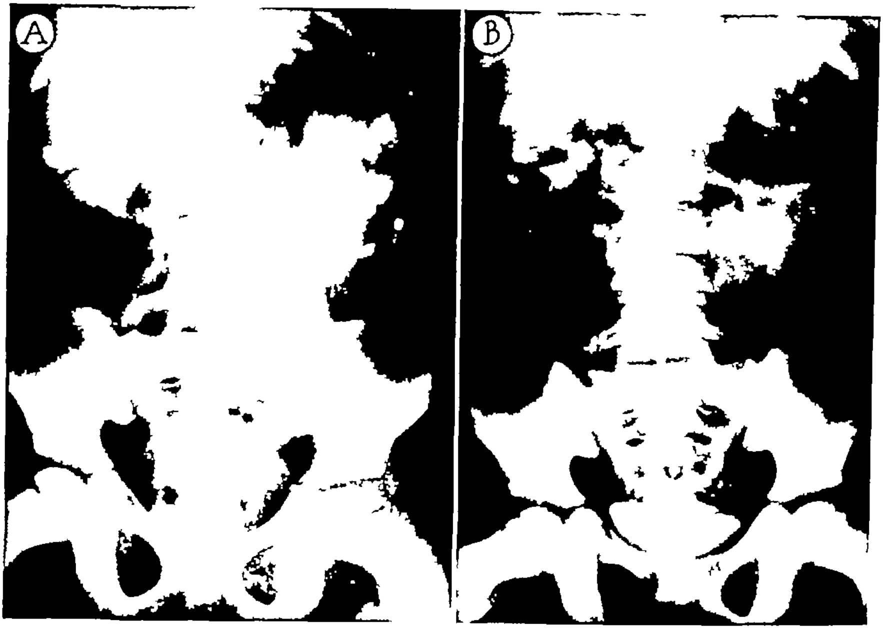

FIG 4

moderate hydronephrosis behind it Retrograde pyeloureterograms confirmed this finding (fig 5, *A*)

Surgical exploration of the right kidney revealed one large polyp approximately 2 cm in length and 0 5 cm in breadth and two smaller polyps approximately 2 5 mm in breadth and length attached to the mucosa of the ureter just below the ureteropelvic junction, in the inferior segment of the right kidney drainage apparatus (fig 5, *B*) These polyps were excised at their base, following which the base of each tumor was lightly fulgurated with the electrical current In order to enlarge the upper portion of the right ureter and afford a better drainage of urine, the lower one third of the two limbs of the bifid ureter were anastomosed side-to-side No drainage tubes or splints were used The incision was closed in layers with only a Penrose drain for drainage The pathologist reported the frozen sections of the polyps prepared at the time of operation to show "benign ureteral mucosal polyp," and the permanent sections as follows "The tissue is seen to be composed of very edematous loose fibrous tissue in which there are a few strands of smooth muscle This is covered by normal transitional epithelium which is denuded in some regions "

Convalescence was uncomplicated and the patient has remained asymptomatic until the present time An intravenous urogram 14 months after surgery is shown (fig 5, *C*)

Case 3 J B T , a 35-year-old white woman had an onset of total gross hematuria with colic in the left flank 10 days prior to the initial visit Furadantin, pyridium and demerol were prescribed, the pain was relieved and the urine became clear grossly The pain in the left costovertebral angle, which radiated into the left lower abdomen and labia, associated with nausea and vomiting,

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THE PROCESS OF URETERAL REPAIR A RECAPITULATION OF THE SPLINTING QUESTION

DAVID M DAVIS

A century ago the great French master of urology, Albarran, recommended that after operations on the kidney, the ureter be splinted with "as large a catheter as possible" for a prolonged period, at least several days He had noted that where drainage of the kidney pelvis had been established, whether it be after removal of stones or after therapeutic drainage of a hydronephrosis or a pyonephrosis, pain disappeared, fever receded, and the patient usually underwent a rapid recovery Yet when the surgeon, encouraged by this dramatic improvement, removed the drainage tube the condition only too frequently soon became just as bad as it had been originally Albarran reasoned—please note this word, reasoned, he did not fall back on some previously established, obviously inadequate doctrine, but he reasoned that if the urine could leave the kidney as easily through the ureter as it had been doing through the drainage tube the patient would remain in a good state of health This conclusion bears the mark of genius, and must be honored as such even though the method of treatment suggested, namely, splinting the intact ureter for several days with a large catheter, proved to be unsuccessful in most cases Modern ureteral surgery has attempted with a large measure of success, to improve on this treatment

Sporadically individual surgeons began to try to enlarge narrowed areas in the ureter by applying the principles of plastic surgery as used in the skin Others, particularly Guy Hunner in the United States, attempted to accomplish the widening by periodic mechanical dilatation to large sizes Edward Keyes incised longitudinally a strictured and scar-surrounded ureter, placed in it for several days a large rubber tube, and obtained an unexpected and dramatic success

Some surgeons splinted their plastic operations with tubes, others did not In the procedure pioneered by Keyes, and later advocated by myself under the name of intubated ureterotomy, a splinting tube is essential to success Darget and Ballenger[1] have recently, going back to Albarran's method, recommended enlarging strictures by forcing large catheters through them, and then leaving the catheter in place two weeks Voices have been raised, sometimes judicially, sometimes rather emotionally, sometimes to attack and criticize splinting, sometimes to defend it The resulting discord has been very confusing to all surgeons who wished to employ the best and most successful methods, and particularly to those beginning their work in ureteral surgery

Fortunately this confusion is now beginning to clear away As usually happens, the clearing is due to the accumulation of precise and detailed knowledge of how the organs and tissues concerned react under all the diverse conditions created by the surgical procedures under investigation I shall try to summarize the significant researches, noting the various manners of approaching the problems,

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Read at annual meeting of the American Association of Genito Urinary Surgeons, Hot Springs Va, May 1-3 1957

[1] Minerva Chir (Turin), 10 432 1955

recurred 10 days following the initial episode and the patient was admitted to the hospital The urine contained a few red blood cells and an occasional white blood cell per high power field Physical examination revealed left flank and lower abdominal tenderness An intravenous pyelogram demonstrated a normal right kidney with no function of the left kidney and several small calcific densities in the region of the lower left ureter (fig 6, *A*) Cystoscopy revealed a normal right ureteral orifice, however, protruding from the left ureteral orifice was a mahogany colored, soft, friable, polypoid mass approximately 5 cm in length This polyp was grasped with forceps and easily extracted from the left ureteral orifice It was fusiform in outline, measuring approximately 8 cm in length and 8 mm in breadth with the distal end tapering to a point Following the extraction of the mass of tissue bloody urine passed from the left orifice Insertion of a left ureteral catheter showed no calculi along the course of the left ureter or in the left kidney A retrograde pyelogram revealed multiple filling defects throughout the entire ureter (fig 6, *B*) The pathological diagnosis was, "Polypoid mass from the ureter, possibly granulation polyp, possibly hemangioma, pedunculated type, which has undergone marked degeneration No evidence of malignant tumor "

Since it could not be determined where this polyp originated and not knowing the pathological process at its base, a nephro-ureterectomy was done Convalesence was uneventful

The removed kidney and ureter were normal except for an elevated whitish area within the ureter, 4 by 2 mm in diameter, located 8 cm distal to the ureteropelvic junction Microscopic study of sections taken from the apparent base of the polyp revealed epithelial hyperplasia with no malignant changes

SUMMARY

Three cases of benign ureteral polyps are added to the 18 reported cases in the literature, making a total of twenty-one There are no recognized signs and symptoms characteristic of ureteral polyps In our first two cases the polyps were found incidental to repair of the ureteropelvic junction and therefore, conservative surgical management was carried out, whereas, in our third case nephro-ureterectomy was performed

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eventually nothing more than a longitudinal linear scar in the ureteral wall, and that, as the inflammatory mass contracted, the muscular wall of the ureter followed it along until at the end of four to six weeks, normal appearing muscle occupied 90 per cent of the circumference of the ureteral wall. Observations in situ showed that this reconstructed and enlarged ureter underwent normal-looking peristalsis, and propelled the fluid contents of the ureter along in an efficient and apparently normal fashion. It was not shown whether the smooth muscle in the wall of the reconstructed part of the ureter was due to an actual proliferation of new fibres or whether it was simply the pre-existing muscle in the ureteral strip stretched out around the splint. At any rate, these conclusions, insofar as they went, have never been disputed, and have in fact been confirmed by all who have repeated the experiments.[10-16]

It was noted, clinically by us[16] and experimentally by Lapides and Caffrey,[11] that if the incised ureter remained in contact with any solid tissue such as the lower pole of the kidney, the peritoneum, or the psoas, quadratus lumborum, or other muscles of the back it became adherent to these structures and suffered distortion of its shape and interference with its proper motility. This could be prevented by surrounding the ureter and any exposed part of the pelvis carefully with fat. The reconstructed ureter then floats surrounded on all sides by the perirenal fat and can adapt itself readily to the up and down movements of the kidney without kinking or tension.

The question as to whether there was actually regeneration of smooth muscle fibres in the reconstructed ureter or not aroused much interest. The most decisive answer was given by Hinman and Oppenheimer[14] who fitted their splint tube with a fine wire mesh through which the ureteral elements had to grow in order to surround the splint. The resulting preparations showed that both epithelium and smooth muscle put forth new cells which grew through the fine interstices of the wire mesh. Most fascinating is the behavior of the smooth muscle fibers after passing the mesh barrier. Upon its far side they find a mass of inflammatory exudate springing from the adjacent fat. The epithelial cells proliferate rapidly, covering the surface of the inflammatory mass where it is in contact with the foreign body, that is, the splint. The smooth muscle cells multiply more slowly, but unerringly make their way around the circumference of the ureter, maintaining their proper distance from the epithelium which has preceded them, and never diverging or spreading out peripherally into the inflammatory mass except just enough to create a layer of smooth muscle of the exactly right thickness to provide the necessary peristaltic activity for the reconstructed ureter. To my mind, this is a phenomenon just as impressive as the regeneration of a complete leg by a lizard after amputation, and of the same general nature. In a tissue culture all body cells show unlimited power of proliferation in all directions, in the body their growth is limited and controlled so that they form themselves

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[10] J Urol, 72 350 1951
[11] J Urol, 73 47, 1955
[12] J Urol, 73 53, 1955
[13] J Urol, 71 274, 1951
[14] J Urol, 76 128 1956
[15] J Urol 74 170 1955
[16] J Urol 66 77 1951

and how the work of many investigators adds up to form a body of knowledge which will serve as the basis for building future advances in ureteral surgery much more intelligently than in the past

The simplest experiments are those seeking satisfactory methods of repairing severed ureters Straight end-to-end, oblique end-to-end, end-to-side, side-to-side, and telescoping end-to-end methods have been suggested, but the oblique end-to-end appears to be unquestionably the best As to suturing, it would seem that delicacy and accuracy are the important matters, since some employ inverting mattress sutures, others everting mattress sutures, still others simple through and through sutures, all with success Very fine catgut is the usual material, but Davalos[2] finds that the finest silk, precisely placed as in arterial suturing, is an excellent material In this type of surgery first intention healing gives a paper-thin scar which can scarcely cause a stricture, and therefore splinting does not seem necessary It is, however, interesting to see that Küss[3] in France and Merget[4] in Germany recommended splint catheters, while Davalos, in the United States, Hryntschak[5] in Austria and Zanaboni and his collaborators[6] in Italy, do without them

In the field of ureterointestinal anastomoses, there is no solidifying of opinion Coffey invariably used splinting catheters Today it is probably that the majority uses splinting catheters when the ureter is anastomosed to the intact sigmoid or rectum, but dispenses with them if the anastomosis is to an isolated ileal loop or colonic segment

The splinting-no splinting debate has raged most furiously about the plastic operations for the correction of ureteropelvic obstructions Not only do different authors have different opinions, but individual authors change their minds from time to time, e g Thomas Gibson[7] of San Francisco The operation of intubated ureterotomy, brought forcefully before the profession in 1943[8] has done more than anything else to stimulate experiments which have made comprehensible the behavior of the ureter when cut, sutured or splinted If we add to this the knowledge derived from the work of those who have tried to bridge actual gaps in the continuity of the ureter, we are now able to predict with great accuracy what will happen in each case, and therefore to choose the best surgical method

In 1948 I published, along with George H Strong and Willard M Drake, Jr [9] the results of experiments on dogs in which a segment of ureteral wall about 2 cm long and representing from ½ to ⅔ the circumference of the ureter was excised The kidney was removed to eliminate urinary drainage from the field, and the ureter was allowed to heal about a splint of rubber tubing The preparations showed that the defect in the ureter was quickly filled with a mass of inflammatory exudate, that the epithelial lining grew around the splint in five or six days, that the inflammatory exudate slowly contracted into what became

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[2] J Urol , 58 22, 1947
[3] Mém de l'Acad de Chir 80 769, 1954
[4] Ztschr f Urol , 49 221, 1956
[5] Ztschr f Urol Chir u Gynäk , 42 268, 1936
[6] Arch Ital di Urol 27 150, 1954
J Urol , 76 708, 1956
[8] Surg Gynec & Obst 76 513, 1943
[9] J Urol , 59 851 1948

spite of the absence of splints Of 11 operations on dogs in which a segment of ureteral wall was removed, four developed strictures, while seven had good results, the lumen of the ureter being described as "adequate", although the authors state frankly that the lumen of the healed ureter was smaller than that of the original ureter Nine human cases of hydronephrosis treated by ureterotomy without splinting gave good clinical results Pre and postoperative pyelograms of 4 cases are published, and the hydronephroses are smaller in spite of the fact that the treated parts of the ureter look quite narrow

The work of Hamm has raised fascinating questions about the ureter, and has done more to stimulate investigators to try to answer them than anything that has happened in a long time Are splints necessary? If used are they harmful? If their effects are both beneficial and harmful, do the beneficial effects outweigh the harmful ones sufficiently to justify their use? Cordonnier and Roane[25] studied the effects of catheters kept in intact ureters for a long time, and found chronic inflammatory manifestations as well as muscular hypertrophy However, these changes disappeared in 4–5 weeks after removal of the catheters In our early work with intubated ureterotomy we noted that if a splint tube was placed so that its lower end lay within the ureter, it might produce a stricture at this point For this reason we began to extend the splint through the entire ureter which did away with this undesirable effect A number of authors have regarded splints as very likely to encourage and propagate infection In my opinion this claim has not been substantiated Infection is favored only if drainage of urine from the kidney or of secretions from the remainder of the wound tract is inadequate With modern antibiotic drugs and correct surgery infection should not contraindicate the use of splints Splinting tubes in contact with urine may become coated or occluded by deposits of calcareous material This complication, which may be very serious, has been combated by three means, first, frequent, or even constant irrigation with acid solutions, second, general measures against stone formation, especially high fluid intake, acid-ash diet, acidifying drugs, and specifically active substances such as acetylsalicylic acid and salicylamide, and third, the use of nonwettable materials for splints, especially polyethylene plastic Polyethylene tubes of suitable diameter are inconveniently rigid, so that some have tried other plastics such as polyvinyl Unfortunately some individuals are allergic to polyvinyl in such a way that an extensive scar-tissue reaction is caused I have reported a case in which both ureters were completely obliterated following intubation with polyvinyl tubes[26]

The above summary shows that there are definite hazards associated with the use of splinting tubes, and it would appear that while most of these hazards can be successfully met with skill and with careful, patient postoperative management, splints should be avoided unless it can be shown that they are really necessary for successful results This of course means that we must know precisely when splints are necessary and when the omission of splinting will not compromise the success of the operation

[25] Surg Clin North Amer , 30 1523, 1950
[26] J Urol 74 747 1955

into functioning organs as though according to some divinely made blue-print The mode of action of these controlling forces is still as mysterious as ever, and today all we can do is to study them and learn as much as possible about the results of their activity

The primary reason for the insertion of a splinting tube has been from the beginning to provide a mold around which the healing process could take place and which would insure that the ureter would, after healing was complete, have a fully adequate caliber Intubated ureterotomy has proved that it is possible in this way to insure that the reconstructed segment of ureter will actually have a caliber much larger than that of the original segment

Inquiring minds always wish to go a step farther, and Frank Hamm of Brooklyn has such a mind He questioned the desirability or the necessity of placing a foreign body splint after incising the ureter A few references to earlier history will be interesting at this point When an epidermoid carcinoma invades beneath the surface, proliferation of its cells produces cyst-like cavities lined by malignant epithelial cells and filled with desquamated epithelial cells Pieces of skin experimentally placed beneath the surface form epithelium-lined cysts I personally observed 35 years ago that if a defect in the perineal urethra was bridged by a large catheter left in until healing was complete, an epithelium lined tube would be produced which would function perfectly adequately for the passage of urine Of course in this region the tube has no muscle in its walls Bengt Johansen[17] buried a rectangular flap or strip of perineal skin to fill such a gap in the urethra, and found that it would form itself into a tube even if no splinting catheter were present Denis Browne[18] using the same principle for the surgical treatment of hypospadias, reports excellent results Stimulated by this work, Reed Nesbit[19] performed experiments in animals which showed that the tube formed in this manner would not have a circumference equal to twice the width of the buried strip, but that the strip ought to have a width about equal to the circumference desired for the new urethral tube—not its diameter This observation may be very pertinent in considering the methods for enlarging the caliber of the ureter

That the ureter will heal very well after a longitudinal incision, with or without sutures, is well known to every surgeon who has performed ureterotomy for stone Unless there are severe complicating factors no stricture results In 1927 Kairis and Perlman[20] performed experiments very like those of Hamm and his collaborators They removed oval pieces of ureteral wall, and noted that the ureter quickly re-established itself, without splints It would seem, however, that there would be little chance of the ureter actually enlarging its caliber as a result of longitudinal incision unless a splint of a caliber larger than that of the original ureter was present Nevertheless Hamm and his collaborators[21-24] operated on both dogs and humans in this manner, and obtained good results in

[17] Acta Chir Scand Supp , 176 1953
[18] Post Grad Med J , 25 367, 1949
[19] J Urol , 64 389, 1950
[20] Ztschr f Urol 21 659, 1927
[21] Proc N Cent Sec Am Urol Assoc , p 52 1954
[22] Tr Am Assoc Gen Urin Surg , 46 109, 1954
[23] J Urol , 73 475 1955
[24] J Urol , 75 43 1956

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[25] Surg Clin North Amer , 30 1523, 1950

[26] J Urol 74 747, 1955

Much light has been cast into this dark but important region by the clever and thorough experiments of Hinman and Oppenheimer[14, 15, 27, 28] They state the problem as follows "The presence of ureteral splint provides a guide for healing The normal sequences involved have been studied but little is known of the aberrations from the norm The current urologic trend is away from splints and tubes, but the physiopathologic reasons for and against such devices have not been made clear"

They made longitudinal incisions in the ureters in the fashion usual in such experiments Some they left alone, without sutures or splints, and in others, omitting splints, they tacked the remaining ribbons of ureter flat against in some cases fat, in others peritoneum and in still others muscle Some have suggested that urine flowing through a healing ureter has a beneficial effect, first by keeping the lumen distended and thereby increasing its caliber, and second by stimulating the peristaltic action of the ureteral muscles and thereby strengthening them Hinman and Oppenheimer, in order to test this thesis, allowed the urine to flow down the ureter freely in some cases, providing a rubber tissue drain to carry it off, and in other cases excluded urine from the operative field altogether by ligating the ureter tightly above the ureterotomy

The results of these experiments are clear-cut I can express them best by quoting the authors "A simple incision heals rapidly and with little fibrosis" Intubation was not necessary if portions of the ureter were not resected Healing was not perfect even after 14 weeks Of significance is the finding that even the simplest incision without any urinary flow or leakage heals with appreciable scarring Urinary flow does not greatly change the pattern of regeneration, but the process takes longer

"The process of healing after a larger defect which is fixed open and unsplinted has (hitherto) only been speculated upon If the ureteral edges are allowed to lie open and free our experimental data indicate that, although healing occurs without significant obstruction in most animals, the ureteral wall is not properly reconstituted If the edges of the ureter are forced to lie free in the retroperitoneal space, and not guided to reapproximate themselves by either splint or suture profuse epithelial overgrowth occurs resulting in sacculations, double lumens and walls composed only of fibrous tissue and bone

"Urinary flow, if adequately drained so that pooling does not occur at the site of repair, does not inhibit repair as much as would be expected However, those defects from which the urine is diverted heal somewhat better than those through which urine flows"

Further experiments with spread out ureterotomies show that healing is least distorted when the ureteral ribbon is completely surrounded by fat Distortion is greater if the ribbon is fastened to peritoneum or muscle, and the ureter becomes adherent and is thereby more or less restricted in its movements

These authors are actively continuing their work on the ureter, and no doubt others are similarly occupied so that we may expect further clarification of details

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[27] J Urol, 76 729, 1956

[28] Surg Gynec & Obst, 103 416, 1956

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In considering the limitations on the usefulness of splints one other important point must be considered It will be remembered that in studying uretero-ureteral anastomosis all investigators found that the best results were obtained when a very precise technique brought about an approximation so accurate that scar was reduced to a minimum However, since there may be in some cases so much actual loss of ureteral substance that approximation of the two ends is impossible, a method of bridging such a gap was eagerly sought As long ago as 1934 Wiseman[29] tried splinting the gap with a catheter left in for 10 to 14 days He found that the splint was quickly surrounded by epithelium, but that outside the epithelium there was nothing but scar tissue, so that the end result was stricture in every case

The remarkable success of intubated ureterotomy suggested that the ureter would reconstruct itself over a splint longitudinally just as well as circumferentially, so that, undeterred by Wiseman's findings, many others have tried to bridge the ureteral gap Sutherland and his co-workers[30] used a polyethylene splint without sutures excising one inch of ureter in some experiments, merely transecting the ureter in others If the splint was removed before the eleventh day complete occlusion followed, from the eleventh to the twenty-third day, severe strictures were the rule, after the twenty-third day, stricturing was described as "minimal " Stricture of some degree obviously occurred in all cases, and the report gives no evidence of any longitudinal smooth muscle regeneration Huffman, McCorkle and Persky[31] carried out similar experiments, except that a segment of ureter was removed in each Careful microscopic preparations showed that the channel occupied by the splint became lined with epithelium, but that smooth muscle never proliferated lengthwise of the ureter The scar tissue outside the epithelium always contracted after the removal of the splint, so that no success was attained Hinman and Oppenheimer,[14] in the course of other experiments noted that sometimes the strip of ureteral wall which was supposed to remain in contact with the splint fell away from it When this happened, the ureteral strip reformed with reduced lumen and complete muscular coat just as in the splintless experiments of Hamm and Weinberg Epithelium grew about the splint forming a complete second lumen, but there was never any proliferation of smooth muscle lengthwise along the splint (fig 1)

One might say in passing that other attempted methods of bridging the gap have failed Hardin[32] substituted polyethylene tubing, segments of veins, and of arteries, all without success Scher and his co-workers[33] and Chauvin, Payan and Jean[34] used polyethylene tubing Scher claims a degree of success in some of his animals, but the period of observation is not long Chauvin found that strictures usually formed at both ends of the polyethylene prosthesis, and that even if the prosthesis was removed after a long time, there was no muscle in the wall of the channel, and strictural contraction was the rule Results were no

[29] Brit J Urol 6 11 1934
[30] South Med J 47 525 1954
[31] J Urol 75 796 1955
[32] A M A Arch Surg 68 57 1954
[33] J Urol 73 987 1955
[34] J d urol 60 871 1954

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[27] J Urol, **76** 729, 1956
[28] Surg Gynec & Obst, **103** 416, 1956

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In considering the limitations on the usefulness of splints one other important point must be considered It will be remembered that in studying uretero-ureteral anastomosis all investigators found that the best results were obtained when a very precise technique brought about an approximation so accurate that scar was reduced to a minimum However, since there may be in some cases so much actual loss of ureteral substance that approximation of the two ends is impossible, a method of bridging such a gap was eagerly sought As long ago as 1934 Wiseman[29] tried splinting the gap with a catheter left in for 10 to 14 days He found that the splint was quickly surrounded by epithelium, but that outside the epithelium there was nothing but scar tissue, so that the end result was stricture in every case

The remarkable success of intubated ureterotomy suggested that the ureter would reconstruct itself over a splint longitudinally just as well as circumferentially, so that, undeterred by Wiseman's findings, many others have tried to bridge the ureteral gap Sutherland and his co-workers[30] used a polyethylene splint without sutures excising one inch of ureter in some experiments, merely transecting the ureter in others If the splint was removed before the eleventh day complete occlusion followed, from the eleventh to the twenty-third day, severe strictures were the rule, after the twenty-third day, stricturing was described as "minimal " Stricture of some degree obviously occurred in all cases, and the report gives no evidence of any longitudinal smooth muscle regeneration Huffman, McCorkle and Persky[31] carried out similar experiments, except that a segment of ureter was removed in each Careful microscopic preparations showed that the channel occupied by the splint became lined with epithelium, but that smooth muscle never proliferated lengthwise of the ureter The scar tissue outside the epithelium always contracted after the removal of the splint, so that no success was attained Hinman and Oppenheimer,[14] in the course of other experiments noted that sometimes the strip of ureteral wall which was supposed to remain in contact with the splint fell away from it When this happened, the ureteral strip reformed with reduced lumen and complete muscular coat just as in the splintless experiments of Hamm and Weinberg Epithelium grew about the splint forming a complete second lumen, but there was never any proliferation of smooth muscle lengthwise along the splint (fig 1)

One might say in passing that other attempted methods of bridging the gap have failed Hardin[32] substituted polyethylene tubing, segments of veins, and of arteries, all without success Scher and his co-workers[33] and Chauvin, Payan and Jean[34] used polyethylene tubing Scher claims a degree of success in some of his animals, but the period of observation is not long Chauvin found that strictures usually formed at both ends of the polyethylene prosthesis, and that even if the prosthesis was removed after a long time, there was no muscle in the wall of the channel, and strictural contraction was the rule Results were no

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[29] Brit J Urol 6 11 1934
[30] South Med J , 47 525 1954
[31] J Urol 75 796 1955
[32] A M A Arch Surg 68 57 1954
[33] J Urol 73 987 1955
[34] J d urol 60 871 1954

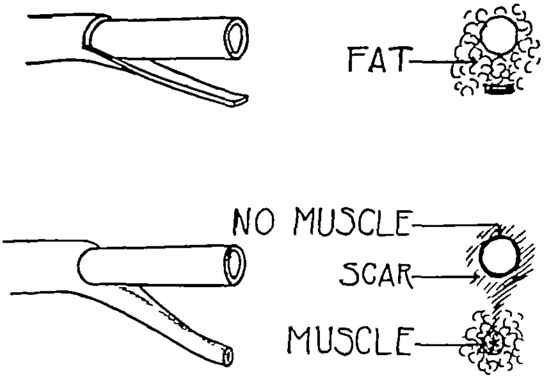

Fig 1 Formation of double lumen when ureteral strip falls away from splint tube No muscle about splint

better if the polyethylene tubing was invested with a segment of vein Schein, Sanders and Hurwitt[35] bridge the gap with an autograft of a segment of fallopian tube, but found this structure unable to conduct enough urine to be of any value

If one digests the results of all this work the strange facts of ureteral regeneration take tangible form, and can be used in planning surgical attack on any kind of ureteral lesion They may be expressed simply as follows

1) If the ureter is incised longitudinally, it will reconstitute itself completely, with epithelial lining and muscular coat, with or without a splint

2) If the ureter is divided transversely, the epithelium will regenerate along a splint or across a suture line, but the muscular coat will never regenerate lengthwise of the ureter, whether the gap be wide or narrow

The reasons for this extremely selective behavior of the ureteral muscle are still entirely unknown, and offer a fascinating field for future research

I believe at this time it is possible to make the following additional statements

a) If the ureter is of normal size or greater before longitudinal incision it will heal without a splint and of the same caliber as originally

b) If the ureter is smaller than normal before longitudinal incision, or if for any reason it is desired to increase its caliber, it is necessary to insert a splint of the size desired for the lumen after healing A complete functioning ureter of increased size with epithelial lining and functioning muscular coat will be obtained

c) If an actual gap in the continuity of the ureter must be bridged, no success can be anticipated from splints or any form of prosthesis yet suggested, and recourse must be had to ileal loop substitution or some form of plastic operation, such as the formation of a tube from a flap of bladder wall

d) If conditions permit the ureteral narrowing to be corrected by a plastic operation, as at the ureteropelvic junction, a splint tube is unnecessary if primary healing occurs If there is doubt of this, as for example if the operative field is already seriously infected, a suitable splint tube is advantageous in that it offers a good chance of retrieving a good result even if the sutures of the plastic operation pull out as a result of the infection

[35] A M A Arch Surg , 73 47, 1956

e) In any kind of an operation on the ureter the result will be better if the ureter is completely surrounded with fat at the end of the operation

f) If splint tubes are used it is better to use rubber or polyethylene tubes avoiding all other kinds unless and until they are proved non-reactive and non-allergenic for all individuals

g) Splint and drainage tubes must be cared for meticulously so long as they are in place to avoid first displacement second occlusion from any cause such as kinking pressure ligation, clamping or stoppage with blood clot or mucus and third sanding Uroconcentration is avoided by copious hydration of the patient, and infection averted by skillful use of antibiotic drugs and adequate drainage of all infection or potentially infected regions

h) If on consideration of all the presently known facts it is correctly concluded that no splint is necessary postoperative care is simplified and the period of convalescence shortened If on the other hand it is decided that a splint is necessary, postoperative care must be meticulous and the splint must be kept in place long enough to accomplish its purpose usually 4 to 6 weeks

I believe we can conclude that the splinting-no splinting debate will end as so many others have ended that is with the realization that there was right on both sides Ureteral splinting is a tremendously valuable procedure because it will solve some surgical problems which cannot be solved in any other way but the use of splints involves enough disadvantages so that they should not be used when they are not necessary

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A PHYSIOLOGICAL APPROACH TO BLADDER IRRIGATION IN GROSS HEMATURIA

J U SCHLEGEL, HANS JØRGENSEN,* A McFADDEN AND W W SCOTT

From the University of Rochester, School of Medicine and Dentistry, Department of Surgery, Division of Urology, Buswell Urological Research Laboratory, Rochester, N Y

The occurrence of frank bleeding from the urinary tract can create a problem in management, since clot formation may block an indwelling catheter or even a normal urethra It seems reasonable to state that it is the desire of the surgeon to maintain an outflow of urine, not only to avoid azotemia but also for a continuous evaluation of the severity of the bleeding Following prostatectomies, gross hematuria to a more or lesser extent is quite common It is consequently a frequent postoperative procedure to use continuous or frequent bladder irrigations to maintain the patency of indwelling catheters by diluting the blood sufficiently to avoid clotting The disadvantages with such procedures are several There is always the danger of inducing an infection, accurate urine volume is hard to estimate due to the presence of a large amount of irrigation fluid, and frequent attendance to maintain the patency of the catheter or catheters is often required From a practical point of view, many of these disadvantages could be overcome if a diuresis of sufficient volume could be established to maintain an internal irrigation It is, however, well known that attempts to hydrate patients following surgery, as well as during conditions involving pain, hemorrhage, and emotional disturbances, will result in over-hydration with retention of fluids, due to antidiuresis [1 7] The antidiuresis present in such cases is supposedly a result of a stimulation of the posterior pituitary, not by virtue of an increase in serum osmolarity, but apparently due to a neurogenic stimulation, the nature of which is uncertain Antidiuresis, however, does not mean that urine volume necessarily has to be low It merely implies that the ratio of solute to water in the urine is

Read at annual meeting of the American Association of Genito Urinary Surgeons, Hot Springs, Va , May 1-3, 1957

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We wish to express our sincere appreciation for the co operation rendered by the Abbott Laboratories, North Chicago, Illinois, which has generously supplied us with the lyophilized urea used in this study We also wish to express our sincere thanks to the nurses who have taken care of the patients in the metabolism room

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[1] Dudley, H F , Boling, E A , LeQuesne, L P and Moore, F D Studies on antidiuresis in surgery Effects of anesthesia, surgery and posterior pituitary antidiuretic hormone on water metabolism in man Ann Surg , **140** 354, 1954

[2] LeQuesne, L P and Lewis, A A G Postoperative retention of water and sodium The kidney Ciba Foundation Symposium, p 193, 1954

[3] Kerrigan, G A , Talbot, N B and Crawford, J D Role of the neurohypophyseal antidiuretic-hormone renal system in everyday clinical medicine J Clin Endocrin , **15** 265, 1955

[4] Leaf, A and Mamby, A R An antidiuretic mechanism not regulated by extracellular fluid tonicity J Clin Invest , **31** 60, 1952

[5] Smith, H W Renal excretion of sodium and water Fed Proc , **11** 701, 1952

[6] Wangensteen, O H and Zimmerman, B Observations on water intoxication in surgical patients Surgery, **31** 654, 1952

[7] Ariel, I M , Kremen, A J and Wangensteen, O H An expanded interstitial (thiocyanate) space in surgical patients Surgery, **27** 827, 1950

increased, so that the concentration of solutes in the urine is higher than in the serum

Forcing water containing no solutes other than dextrose will obviously lead to a disturbance of the homeostasis with dilution of the serum electrolytes The presence of glucose in the infusion is, in this respect, of no value, since it is metabolized to CO_2 and water

Salt must naturally be considered a solute, but, since sodium retention often prevails following surgery, due to active reabsorption possibly in the proximal tubule of the kidney, it is consequently not available quantitatively for excretion in the urine Therefore, the postoperative administration of large amounts of fluids containing salt would not lead to any dilution of body fluids but to an expansion, which again implies that the urine volume would remain low and that the patient would become edematous It is well known that during antidiuresis the urine volume is a direct result of the amount of solutes excreted[1] [8] One solute which apparently is handled rather passively by the kidney and which will be distributed evenly over total body water, thus not causing any change in the compartmental distribution, is urea It has been shown by us that antidiuresis following surgery can be completely overcome by the administration of urea as a 4 per cent solution[9] Its addition to infusion solutions of 5 per cent dextrose in water given patients with relatively normal kidney function will not lead to dehydration and will maintain homeostasis in regard to water and electrolytes In meeting the obligatory requirement of the kidney during antidiuresis, it is important to realize that it is not the volume given that is of particular significance, but the ratio of solute to water which has to be adjusted to the immediate functional capacity of the kidney This, in reality, means that it is feasible to give large amounts of fluid, provided that it contains the proper amount and kind of solute, and thus obtain a urine output which can be adjusted at will to suit the purpose for which it is intended A more thorough study of the basic mechanism involved has been published elsewhere[9] In this paper, a practical utilization of the basic physiological phenomenon of post-traumatic antidiuresis is presented as it occurs following suprapubic prostatectomies

MATERIAL AND METHODS

Forty prostatectomy cases were used in this study All the patients had at time of surgery a phenolsulfonphthalein within normal limits and a nonprotein nitrogen and blood urea nitrogen likewise within normal limits Some of the patients also had urea clearances which varied between 50 and 100 per cent of normal a few of these had decreased kidney function when first seen, none of them had frank renal insufficiency at time of surgery

The majority of the patients were followed in a room with constant temperature and humidity, they were on a diet of known composition, and accurate records were kept of their intake and output Serum and urine chemistries were

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[8] Brodsky, W A IV Determination of water and electrolyte excretion during osmotic diuresis in hydropenic man Meth Med Res , 5 192, 1952

[9] Schlegel, J U Eldrup-Jørgensen, S and Stone, H Studies in metabolism of trauma I Maintenance of homeostasis during antidiuresis Ann Surg , 146 12 1957

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[5] Smith, H W Renal excretion of sodium and water Fed Proc , **11** 701, 1952

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Na ...ent ...nce	Serum Osmolarity (Corrected Per cent Change)	BUN Change mg%	Weight Change Grams
−2.1	−1.4	+56.3	−500
−2.1	−0.7	+34.7	−1100
−0.2	+1.5	+26.3	−800
+2.5	+6.0	+65.5	−900
−1.6	−0.3	+41.7	−1350
−0.4	+2.5	+68.9	−1650
−1.8	−1.1	+48.7	−1750
+3.6	+1.0	+61.3	−1400
−1.7	+1.4	+60.5	−1150
+4.0	+4.2	+35.3	−1900
+0.2	+1.3	+49.9	−1250

...intake)

+2.4	−1.4	+48.5	−450
−3.2	−1.4	+61.3	−500
−0.3	+2.2	+39.2	−1400
−2.6	−6.1	+50.1	−950
+1.1	+2.1	+44.8	−550
−0.5	−0.9	+48.8	−770

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determined daily, and total balance studies in regard to nitrogen, sodium, potassium and water were carried out on a 24-hour basis The patients were weighed once a day This study deals only with the first 24-hour period following surgery, and the weights recorded are those obtained immediately prior to surgery and 24 hours following A few patients were followed as controls and received approximately 2000 cc 5 per cent dextrose in water intravenously in the first 24-hour period following surgery The other patients received 4 per cent urea added to infusion solutions of 5 per cent dextrose in water, the majority of the patients received 4000 cc intravenously in the first 24-hour period, and a few received only 3000 cc In order to evaluate the balances more accurately and avoid dilution of the administered solutes, the patients were all kept on no oral intake for the first 24 hours following surgery The methods used for determination of serum and urine chemistries have been published elsewhere [9]

Urea was in all instances given in isotonic solutions of glucose (or saline) since even isotonic solutions of urea in water (1 8 per cent) can cause hemolysis [10]

The intravenous fluids containing urea were prepared by using lyophilized urea which was dissolved in the infusion solution immediately prior to the administration Prepared in this way, it is stable for at least a 24-hour period It is necessary, however, to keep the urea in lyophilized, dry form until such time that it can be used, since otherwise it will absorb water and decompose, forming ammonia Heat rapidly decomposes urea with the formation of ammonia, and consequently solutions containing urea can not be autoclaved The lyophilized preparation that we have used has been kindly made available to us through the co-operation of the Abbott Laboratories

RESULTS

None of the patients receiving urea added to the infusion solutions had any untoward effects, all had an excellent output and did not require catheter irrigation since clotting was prevented by their high urinary output Seven of the 40 patients had primary closure of the bladder All seven received approximately 4000 cc intravenous fluids with 4 per cent urea, and no complications due to bleeding were encountered All 40 patients did quite well, there were no fatalities, and no significant clinical difference between the patients who received urea and the few who did not receive urea added to the infusion solutions but only received 2000 cc intravenous fluids

In table 1 are given some of the data obtained from some of the patients receiving approximately 4000 cc intravenously and 3000 cc intravenously, respectively It will be noticed that there was no significant difference in the percentage return of the administered fluids nor in the percentage return of the administered urea Sodium balance varied considerably from individual to individual but was negative in most instances Although there were minor deviations in the serum sodium and serum osmolarity, the over-all changes were extremely small and, in general, it can be stated that no changes in serum electro-

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[10] Javid, M and Settlage, P Effect of urea on cerebrospinal fluid pressure in human subjects A preliminary report J A.M A 160 943 1956

TABLE 1 *Patients receiving 5 per cent dextrose infusions with 4 per cent urea*

Subject	Intake H_2O cc	Urine Per cent of Intake	Urea Excreted Per cent of Intake	Na Balance mEq	Serum Na Per cent Change	Serum Osmolarity (Corrected Per cent Change)	BUN Change mg%	Weight Change Grams
			a (appr 4000 cc Intake)					
E C	4000	102.0	73.6	−126	−2.1	−1.4	+56.3	−500
H. D	4000	92.7	54.0	−97	−2.1	−0.7	+34.7	−1100
C H	3845	95.3	69.7	−29	−0.2	+1.5	+26.3	−800
G E	4210	86.2	56.2	−24	+2.5	−6.0	+65.5	−900
R L	4004	100.0	72.4	−118	−1.6	−0.3	+41.7	−1350
H F	4000	81.5	46.5	+55	−0.4	+2.5	+68.9	−1650
A L	4000	93.2	71.5	−108	−1.8	−1.1	+48.7	−1750
C S	4100	72.1	36.7	−9	+3.6	+1.0	+61.3	−1400
P M	4000	83.1	56.3	−37	−1.7	+1.4	−60.5	−1150
H F	4000	93.8	54.5	+29	+4.0	+4.2	+35.3	−1900
Mean	4016	90.0	59.1	−46.4	+0.2	+1.3	+49.9	−1250
			b (appr 3000 cc Intake)					
C W	2750	87.3	57.3	+15	+2.4	−1.4	+48.5	−450
H. H	2590	93.6	52.4	−51	−3.2	−1.4	+61.3	−500
I L	3350	103.0	65.1	−18	−0.3	+2.2	+39.2	−1400
H W	3300	87.1	66.2	−6	−2.6	−6.1	+50.1	−950
J A	3000	77.4	49.6	+13	+1.1	+2.1	+44.8	−550
Mean	2998	89.7	58.1	−9.4	−0.5	−0.9	+48.8	−770

lytes took place even with fluid loads as high as 4000 cc, if 4 per cent urea was added to the infusion solutions of 5 per cent dextrose in water. Increases in blood urea nitrogen were naturally observed but, as previously stated, this had no untoward effect and usually declined very rapidly throughout the next two or three days. The weight losses were significantly higher than those obtained in the control patients not receiving urea, and were more equivalent to the weight loss observed in normal individuals on nothing by mouth and on bed rest for 24-hour periods[9]. It thus appears that the administration of high fluid loads containing 4 per cent urea, on the day of surgery, is a perfectly safe and harmless procedure which will not lead to any water intoxication in patients with relatively normal kidney function.

In table 2 are presented the results obtained in 8 patients receiving an average of 2200 cc of 5 per cent dextrose in water, and it will be noted that the percentage volume return was considerably lower than in the patients receiving even the double amount but with 4 per cent urea. The sodium balance in these cases is negative, as in most of those receiving 4 per cent urea, but in general exceeds the negativity in the cases receiving urea. However, this does not appear significant and in general one might state that the addition of urea to the infusion solutions,

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E. C.	4110	102.0	73.6	−125	−2.1	−1.4	+50.8	−500
H. D.	4070	82.7	54.0	−97	−2.1	−0.7	+34.7	−1100
C. H.	3545	95.3	69.7	−29	−0.2	+1.5	−26.8	−800
G. E.	4200	88.2	56.2	−24	+2.5	+6.0	+65.5	−900
R. L.	4104	100.0	72.4	−118	−1.6	−0.3	+41.7	−1850
H. F.	4110	81.5	46.5	+55	−0.4	+2.5	+68.9	−1650
A. L.	4070	93.2	71.5	−108	−1.8	−1.1	+48.7	−1780
C. S.	4000	72.1	38.7	−9	+1.6	+1.0	+61.8	−1400
P. M.	4010	88.1	56.3	−37	−1.7	+1.4	+60.5	−1150
H. F.	4003	93.8	54.5	+29	+4.0	+4.2	+85.3	−1900
Mean	4015	91.0	59.1	−46.4	+0.2	+1.3	+49.9	−1230
			b (appr. 3000 cc Intake)					
C. W.	2750	87.3	57.3	+15	+2.1	−1.1	+18.5	−130
H. H.	2593	96.6	52.4	−51	−3.2	−1.1	+31.3	−500
L. L.	3250	106.0	65.1	−18	−0.3	+2.2	+39.2	1100
H. W.	2710	87.1	66.2	−6	−2.6	−0.1	+50.1	950
J. A.	3111	77.4	49.6	+13	+1.1	+2.1	+11.8	550
Mean	[illegible]	90.7	58.1	−9.4	−0.5	−0.0	+18.8	770

lytes took place even with fluid loads as high as 4000 cc, if 4 per cent urea was added to the infusion solutions of 5 per cent dextrose in water. Increases in blood urea nitrogen were naturally observed but, as previously stated, this had no untoward effect and usually declined very rapidly throughout the next two or three days. The weight losses were significantly higher than those obtained in the control patients not receiving urea, and were more equivalent to the weight loss observed in normal individuals on nothing by mouth and on bed rest for 24-hour periods.[3] It thus appears that the administration of high fluid loads containing 4 per cent urea, on the day of surgery, is a perfectly safe and harmless procedure which will not lead to any water intoxication in patients with relatively normal kidney function.

In table 2 are presented the results obtained in 8 patients receiving an average of 2200 cc of 5 per cent dextrose in water, and it will be noted that the percentage volume return was considerably lower than in the patients receiving even the double amount but with 4 per cent urea. The sodium balance in these cases is negative as in most of those receiving 4 per cent urea, but in general exceeds the negativity in the cases receiving urea. However, this does not appear significant and in general one might state that the addition of urea to the infusion solutions,

determined daily, and total balance studies in regard to nitrogen, sodium, potassium and water were carried out on a 24-hour basis The patients were weighed once a day This study deals only with the first 24-hour period following surgery, and the weights recorded are those obtained immediately prior to surgery and 24 hours following A few patients were followed as controls and received approximately 2000 cc 5 per cent dextrose in water intravenously in the first 24-hour period following surgery The other patients received 4 per cent urea added to infusion solutions of 5 per cent dextrose in water, the majority of the patients received 4000 cc intravenously in the first 24-hour period, and a few received only 3000 cc In order to evaluate the balances more accurately and avoid dilution of the administered solutes, the patients were all kept on no oral intake for the first 24 hours following surgery The methods used for determination of serum and urine chemistries have been published elsewhere [9]

Urea was in all instances given in isotonic solutions of glucose (or saline) since even isotonic solutions of urea in water (1 8 per cent) can cause hemolysis [10]

The intravenous fluids containing urea were prepared by using lyophilized urea which was dissolved in the infusion solution immediately prior to the administration Prepared in this way, it is stable for at least a 24-hour period It is necessary, however, to keep the urea in lyophilized, dry form until such time that it can be used, since otherwise it will absorb water and decompose, forming ammonia Heat rapidly decomposes urea with the formation of ammonia, and consequently solutions containing urea can not be autoclaved The lyophilized preparation that we have used has been kindly made available to us through the co-operation of the Abbott Laboratories

RESULTS

None of the patients receiving urea added to the infusion solutions had any untoward effects, all had an excellent output and did not require catheter irrigation since clotting was prevented by their high urinary output Seven of the 40 patients had primary closure of the bladder All seven received approximately 4000 cc intravenous fluids with 4 per cent urea, and no complications due to bleeding were encountered All 40 patients did quite well, there were no fatalities, and no significant clinical difference between the patients who received urea and the few who did not receive urea added to the infusion solutions but only received 2000 cc intravenous fluids

In table 1 are given some of the data obtained from some of the patients receiving approximately 4000 cc intravenously and 3000 cc intravenously, respectively It will be noticed that there was no significant difference in the percentage return of the administered fluids nor in the percentage return of the administered urea Sodium balance varied considerably from individual to individual but was negative in most instances Although there were minor deviations in the serum sodium and serum osmolarity, the over-all changes were extremely small and, in general, it can be stated that no changes in serum electro-to their intravenous fluids are more identical with what appears to be a normal weight loss in a patient who is starved for a 24-hour period

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[10] Javid, M and Settlage, P Effect of urea on cerebrospinal fluid pressure in human subjects A preliminary report J A M A , **160** 943, 1956

In patients receiving 4 per cent urea added to infusion solutions of 5 per cent dextrose in water, there is in general no change in the serum electrolytes as compared to the patients receiving approximately 2000 cc of intravenous fluids in the form of 5 per cent dextrose in water and no urea added This holds true even with fluid intakes as high as 4000 cc in the 24-hour period immediately following surgery

We have not found that the administration of urea changes the excretion of sodium, and this is in accordance with what has been observed by other investigators[13-15] Therefore, sodium chloride is given only in small amounts the day of surgery The addition of approximately 5 gm of salt usually will lead to zero sodium balance except in cases where severe sodium retention existed prior to surgery

It can be concluded that the addition of 4 per cent urea to the standard dextrose in water infusion enables us to administer large fluid volumes without the risk of water intoxication The increased urinary output thus obtained appears to be a valuable aid in the management of patients following suprapubic prostatectomy

It may be added that we have recently utilized the principles described in other cases of gross hematuria with equal success

SUMMARY

Postoperatively, patients can safely be given large amounts of intravenous infusions of 5 per cent dextrose in water without risking any dilution of body fluids provided that a relatively normal kidney function is present and that a solute such as urea is added in a concentration of approximately 4 per cent

Without the addition of urea, water retention is evident even with moderate fluid loads

The high urinary output which can be obtained in this fashion has been found most helpful in urological surgery where gross hematuria is encountered

[13] Mudge, G H, Foulks, J and Gilman, A Effects of urea diuresis on renal excretion of electrolytes Am J Physiol, 158 218, 1949

[14] Seldin, D W and Tarail, R Effect of hypertonic solutions on metabolism and excretion of electrolytes Am J Physiol 156 160, 1949

[15] Miller, H R and Feldman, A Prolonged use of massive doses of urea in cardiac dropsy Arch Int Med, 49 964 1932

TABLE 2. *Patients receiving 5 per cent dextrose infusions not containing urea*

Subject	Intake H_2O cc	Urine Per cent of Intake	Na Balance mEq	Serum Na Per cent Change	Serum Osmolarity (Corrected) Per cent Change	Weight Change Grams
W. M.	2060	21.9	−24	−3.5	−3.2	−400
E. L.	2060	47.9	−78	−5.6	−5.4	+400
D. V.	2250	40.4	−116	−3.2	−3.1	−1000
E. V.	2080	42.8	−102	−2.4	−4.5	−1500
C. G.	2190	49.9	−71	−3.8	−4.3	−400
W. L.	2559	25.9	−39	−4.2	−3.9	−300
W. S.	2665	84.7	−86	−0.8	−2.1	−550
J. C.	2090	35.6	−57	−1.6	−3.8	−650
Mean	2244	43.6	−72	−3.1	−3.8	−550

even when large amounts of fluid are given, does not significantly alter the sodium metabolism. In the control cases, it will be seen that a slight dilution did occur with a change in sodium and osmolarity indicative of a slight degree of water intoxication. Parallel to this is seen a weight change which, although negative, is less so than in the patients receiving the 4 per cent urea infusion solutions.

From these results, it appears that up to 4000 cc of 5 per cent dextrose in water containing 4 per cent urea can safely be given to patients on the day of surgery, provided that their kidney function is relatively normal. This also applies to cardiac patients, of whom there were several included in this study. The reason for this is that urea is rapidly distributed over total body water and will thus not lead to any shift in the compartmental distribution of fluid, especially to no increase in circulating blood volume. The usual contraindication for rapid administration of intravenous fluids to cardiac patients must naturally still be borne in mind.

Larger amounts of sodium should not be given, since this will be retained, however, a slight negative sodium balance will occur unless an amount of approximately 5 grams of sodium chloride is administered. Practically no sodium loss occurs, following surgery, in patients who, beforehand, have been on a low sodium diet or who have sodium retention for other reasons, therefore no sodium should be given such patients postoperatively.

DISCUSSION

The main purpose of this work is to show the practical application of a physiologically well established fact. The average weight loss as reported by other authors following surgery is considerably less than the weight loss which will be encountered in normal individuals who are receiving no food for a period of 24 hours, and who are on bed rest and receiving intravenous fluids only.[9, 11, 12] The weight losses that we find in patients who have received 4 per cent urea added

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[11] Moore, F. D.: The significance of weight changes after trauma (editorial). Ann. Surg., 141: 141, 1955.

[12] Paquin, A. J., Jr.: The rate of body weight loss following surgical stress of uniform intensity. Ann. Surg., 141: 383, 1955.

(fig 1) In spite of the extensive bladder deformity, there was no ureteral obstruction

A 16F cystoscope passed easily The urine was bloody but cleared with one or two washings Inspection of the bladder revealed an extensive lesion projecting from the right side as a domelike elevation. It had a solid appearance and was dusky red with scattered blackened areas that appeared to be caused by old hemorrhage. The entire surface was irregularly edematous but no areas of ulceration or exudate were seen In contrast most of the *left* half of the bladder presented normal-appearing mucosa

The clinical, roentgen and cystoscopic findings indicated that the condition was an an acute intraperitoneal inflammatory process (most probably appendicitis) with extension to the bladder Exploratory laparotomy was advised and performed as an emergency in the late evening on the day of admission.

Operation A low right paramedian incision was made Considerable edema of of the abdominal wall was noted The peritoneal cavity contained a considerable quantity of clear fluid culture of this fluid later was reported to be sterile. Inspection revealed no evidence of intestinal disease The appendix was identified and appeared to be normal Pronounced retroperitoneal edema on the right side had elevated the posterior peritoneum.

Palpation of the bladder intraperitoneally revealed a firm smooth mass involving the right side The bladder was not fixed Because the bladder apparently

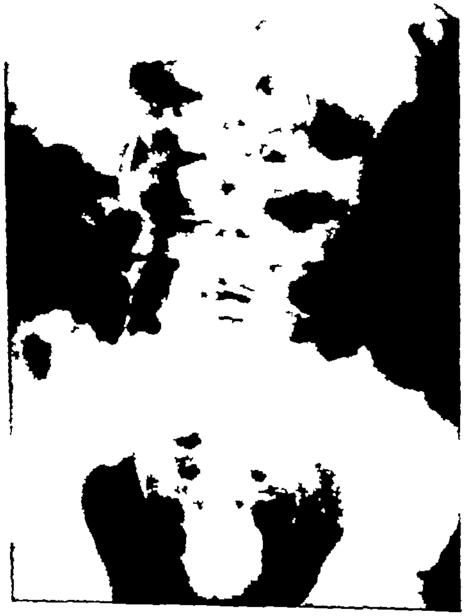

Fig 1 Intravenous urogram Note unusual bladder deformity Upper urinary tract appears normal and there is no ureteral obstruction

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ACUTE NECROTIZING ANGIITIS OF THE BLADDER
REPORT OF A CASE

WILLIAM J ENGEL AND LAWRENCE J McCORMACK

From the Departments of Urology and of Pathology, The Cleveland Clinic Foundation and The Frank E Bunts Educational Institute, Cleveland, Ohio

Necrotizing angiitis as a pathological entity has attracted considerable interest in the past two decades Because sensitization to various drugs, notably the sulfonamides, is an established etiologic factor, one may expect to encounter this disease more commonly in this age of enthusiastic and varied drug administration The following report concerns a case of necrotizing angiitis in which the predominant clinical manifestations involved the bladder, with symptoms including hematuria and acute abdominal pain It is probable that the pathological process involved other organs as well as the bladder Sensitization to the sulfonamide gantrisin is strongly suggested as the causative agent

CASE REPORT

A 13-year-old boy was admitted to the hospital for emergency treatment on January 23, 1955, because of abdominal pain and frequency of urination with terminal pain followed by gross hematuria

About 7 or 8 days previously the patient had an illness described as "the flu" with a temperature to 102F and associated with sore throat He was given one tablet of gantrisin every four hours for five doses Four days later, the temperature returned to normal, he felt better, and he returned to school The night before admission to the hospital he noted pain on urination which was most extreme when terminating the act Urinary frequency became more pronounced and finally gross hematuria was noted on the morning of admission The patient also had had some abdominal pain with loss of appetite but no nausea or vomiting

On admission, the patient's temperature was 98 6F, pulse rate 90, blood pressure 120/80 mm Hg The boy appeared somewhat pale but not severely ill The ears, nose, throat, and chest were normal Abdominal palpation revealed diffuse lower abdominal tenderness, most marked over the right lower quadrant where considerable muscle guard was noted Definite rebound tenderness was elicited The penis and testicles were normal Rectal examination revealed tenderness with suggestive induration high above the prostate, chiefly on the right side

The urine was grossly bloody The leukocyte count was 10,450 with 89 per cent neutrophils The blood urea was 21 mg per 100 cc

A plain roentgenogram of the abdomen was negative The intravenous urogram showed prompt excretion of the contrast medium, the kidney pelves and ureters were outlined satisfactorily and appeared to be normal (fig 1) There was no demonstrable ureteral obstruction The bladder shadow, however, showed an unusual deformity involving chiefly the right side and dome of the bladder

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Read at annual meeting of the American Association of Genito Urinary Surgeons, Hot Springs, Va , May 1-3, 1957 (fig 1) In spite of the extensive bladder deformity, there was no ureteral obstruction.

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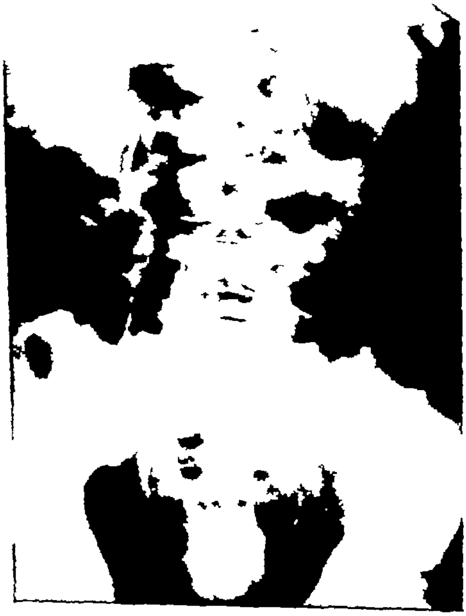

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Read at annual meeting of the American Association of Genito Urinary Surgeons, Hot Springs, Va , May 1-3 1957 necrotizing process also involved the blood vessels of the fatty envelope of the bladder Pathological diagnosis was acute necrotizing angiitis of a hypersensitivity type

The convalescence was without serious event He had a low-grade fever (maximum temperature 101F) which persisted for 14 days A cystogram made on the twelfth day after operation showed a small bladder but little of the deformity noted on the urogram

On the seventeenth day following operation a cystoscopic examination showed an essentially normal bladder except for edema surrounding the suprapubic catheter The suprapubic catheter was removed and the sinus closed by suture The wound healed promptly and the patient left the hospital three days later

Past history of this patient, we believe, is of importance as offering a possible explanation for the development of his disease He has a history of allergy and had received treatment in the Department of Allergy for hay fever, bronchial asthma and allergic rhinitis since the age of 8 years

In October 1954 he had an illness associated with headache, a mild chill followed by fever (temperature to 101 6F), sore throat and some pain in perineum and penis The blood count was normal and the urinalysis revealed only an occasional white blood cell Examination in the Department of Otolaryngology revealed the presence of a purulent maxillary sinusitis and roentgen examination showed cloudiness of the left ethmoid and both frontal sinuses He was advised to take gantrisin, 2 gm immediately, to be followed by 0 5 gm every 6 hours for a week This medication was taken according to instructions, the patient's condition improved and he returned to school He apparently remained well until the time of the present hospital admission It will be recalled that seven or eight days before this hospital admission the patient had been given 5 tablets of gantrisin because of a sore throat This history immediately suggests the possibility of a hypersensitivity reaction to gantrisin as the explanation for his necrotizing angiitis

This patient apparently remained well until December 28, 1955, when he was seen again because of diarrhea with three to four watery stools a day and recent bloody stools There was little if any abdominal pain and no nausea or vomiting There had been no urinary symptoms and the urine was clear There was a moderate anemia

He was admitted to the hospital for gastrointestinal study (E N Collins, M D , Department of Gastroenterology) on January 9, 1956 Urinalysis at that time was entirely negative Colon x-ray studies revealed findings suggesting chronic ulcerative colitis although proctoscopic examination revealed no local signs of this disease He was given blood transfusions and placed on appropriate medical management, his condition improved

A recurrence of the bloody diarrhea necessitated readmission to the hospital on August 16, 1956, for further transfusions and medical management He continued to have trouble, believed to be due to angiitis (periarteritis nodosa) involving the gastrointestinal tract and probably diffuse disease as well In November 1956 he was started on ACTH, 10 units twice weekly intramuscularly and meticorten 2½ mg daily In addition to this he was given 500 mg of chloro was the site of primary disease, the peritoneum was closed and the incision extended downward suprapubically to expose the bladder During this procedure extensive perivesical edema was observed chiefly on the right side where it extended laterally for several inches

When the bladder was opened, a dusky reddish-black, extensive lesion on the right side was exposed On palpation it was firm and edematous but not hard or nodular The bladder wall in this area was greatly thickened Frozen sections of specimens for biopsy taken from several areas were reported to show only inflammatory changes A generous full-thickness piece of the lesion was removed for permanent section pathologic study following which the bladder was closed around a No 22 Foley bag, suprapubic drainage catheter The wound was closed in layers

Pathological report The surgical biopsy showed major morphologic changes limited to the interstitial tissues of the bladder and its fatty covering A marked infiltration of polymorphonuclear leukocytes and extravasated erythrocytes occurred in these areas with some concentration around blood vessels A profuse involvement of the small arteries and veins, evidenced by a smudging and haziness of their outlines and infiltration by polymorphonuclear leukocytes, was present (fig 2, *A*) The phosphotungstic acid hematoxylin stain (Mallory) demonstrated large amounts of fibrin within the smudged vessel walls, as evidenced by the intense bluish-purple coloration (fig 2, *B*) No thrombosis of vessels was noted The smooth muscle fibers of the bladder were not necrotic, but were focally separated by edema and extravasated red cells The acute

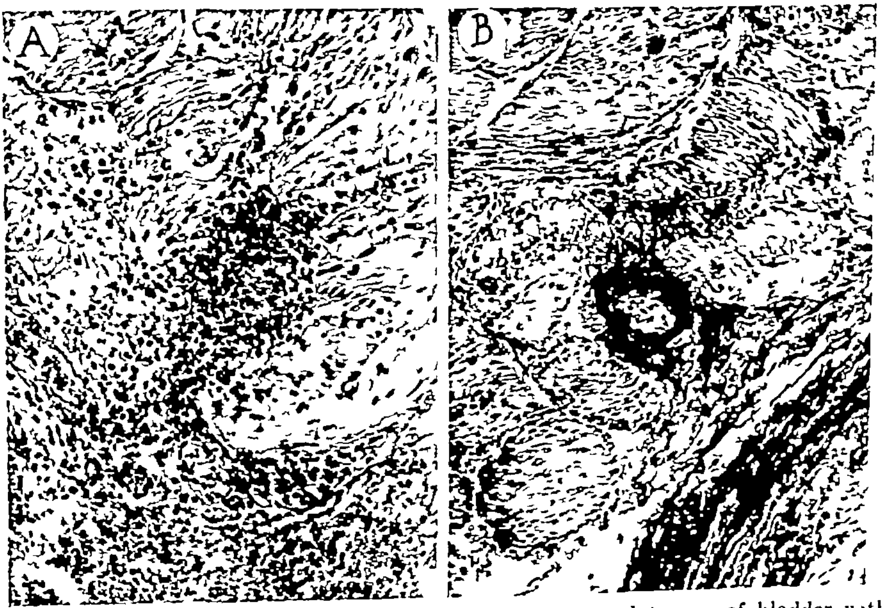

FIG 2 *A*, section demonstrates three vessels in interstitial tissues of bladder with smudging of walls and perivascular infiltration of polymorphonuclear leukocytes Interstitial hemorrhage also is present Hematoxylin eosin methylene blue stain, ×185 *B* special stain demonstrating perivascular accumulation of fibrin Mallory's phosphotungstic acid hematoxylin stain, ×185

was started were normal, whereas nine days after sulfa administration lesions of periarteritis nodosa were present in the scrotum and widespread throughout the body. It is now generally accepted that this disease, by whatever title, can result from anaphylactic type of hypersensitivity reaction.

Hypersensitivity angiitis in man has been reported from sulfonamides as well as other substances such as dilantin, thiourea, organic arsenicals, Lugol's iodine, the antibiotics, aspirin. Rich[5] describes an anaphylactic type of sensitization due to the production of antibodies which react specifically to a foreign antigen. In this type the specific antigen causes death of cells as the result of vascular damage which interferes with the nutrition of the cell. The effects are upon the vascular endothelium, causing endothelial necrosis; on smooth muscle, producing spasmodic contraction, and on the collagen fibers which undergo degeneration and fragmentation and altered interfibrillary substance.

It has been shown that sulfonamides can attach to plasma proteins and the complex so formed can act as an antigen to sensitize the body anaphylactically to the sulfa radical.[6-8] In such cases the administration of sulfa drugs may produce hypersensitivity angiitis and continued administration may produce a fatal reaction. Rich[5] reports that at the Johns Hopkins Hospital there were but six cases of periarteritis nodosa reported in necropsies between the years 1916 and 1935. Sulfonamides were introduced in 1936 and in the years between 1936 and 1946 38 cases were found. In studies on necrotizing angiitis, Knowles, Zeek and Blankenhorn[9] found a direct relationship between sulfonamide therapy and hypersensitivity angiitis in seven of 10 cases which came to necropsy. Hematuria had been present in 5 of these 10 cases and was attributed to the renal lesions. No cystoscopic examinations had been performed. Repeated hematuria was also present in five of 13 cases of primary periarteritis nodosa. In one patient, these authors mention that the vascular lesions led to necrosis of the bladder wall and pelvic peritonitis.

In a study of 76 fatal cases following sulfonamide therapy, French[10] reported finding typical lesions in practically all organs of the body, including the bladder but this organ was not routinely examined.

The sites of predilection of necrotizing angiitis are the kidneys and heart as well as the pulmonary vessels and spleen. It appears to be uncommon in the pancreas and gastrointestinal tract. It is not unexpected that the kidneys would be prominently affected in any acute vascular disease. Thus a necrotizing glomerulitis is a frequent finding in cases terminating fatally.

In the case we have presented, the histologic findings are identical with those quine a day and 50 mg of marsilid every other day The father reports that the patient occasionally has had mild diarrhea but feels better generally, is gaining weight and has been in school every day At no time has there been any recurrence of bladder trouble or hematuria

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[5] Rich, A. P.: Hypersensitivity in disease. Harvey Lectures 1946-1947, pp. 106-147.

[6] Schönholzer, G.: Die Bindung von Prontosil an die Bluteiweisskörper. Klin. Wchnschr. 19: 790, 1940.

Davis, B. D.: Binding of sulfonamides by plasma proteins. Science 95: 78, 1942.

[8] Wedum, A. G.: Immunological specificity of sulfonamide azoproteins. J. Infect. Dis., 70: 173, 1942.

[9] Knowles, H. C., Jr., Zeek, P. M. and Blankenhorn, M. A.: Studies on necrotizing angiitis; periarteritis nodosa and hypersensitivity angiitis. A.M.A. Arch. Int. Med. 92: 789, 1953.

[10] French, A. J.: Hypersensitivity in the pathogenesis of the histopathologic changes associated with sulfonamide chemotherapy. Am. J. Path. 22: 679, 1946.

DISCUSSION

Although necrotizing angiitis has received considerable attention in recent medical literature we have been unable to find another case in which the urinary bladder was the chief organ involved in its clinical manifestations

Some confusion still exists in the terminology of the angiitides The term, periarteritis nodosa was introduced in 1866 by Kussmaul and Maier[1] for a degenerative disease of arteries characterized by grossly visible nodes along the arteries at autopsy Since this time, other vascular lesions of similar type have been described with such terms as rheumatic arteritis, polyvasculitis, temporal arteritis, necrotizing arteriolitis, allergic granulomatous angiitis

Zeek[2] suggests necrotizing angiitis as the generic term and would classify these cases into the following groups

1) Periarteritis *nodosa—a recurrent or chronic progressive necrotizing inflammatory* disease involving chiefly muscular type arteries

2) Hypersensitivity angiitis—an acute necrotizing inflammation in and around the smallest arteries and veins of the viscera, connective tissue and skin Larger vessels are involved in advanced cases Necrotizing glomerulitis is often found and *fulminating renal failure may cause death*

3) Rheumatic arteritis—an acute inflammation with minimal fibrinoid necrosis which is always associated with rheumatic fever

4) Allergic granulomatous angiitis—a chronic disease in which the vascular disease is part of a generalized granulomatous condition Vascular occlusion may occur in the late stages

5) Temporal arteritis—a rather rare self-limited disease characterized by granu*lomatous inflammation and fibrinoid necrosis involving the temporal arteries* most frequently

In 1942 Rich[3] emphasized the role of hypersensitivity in periarteritis nodosa when the disease was observed in patients receiving antiserum for pneumonia He also noted similar lesions in a patient from the surgical service who had received sulfathiazole intravenously but no serum Later in the same year he reported periarteritis nodosa in a patient receiving sulfathiazole only[4] In this case scrotal skin sections five months and one week before sulfonamide therapy

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[1] Kussmaul, A and Maier, R Ueber eine bisher nicht beschriebene eighenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht Deutsch Arch f klin Med , 1 484, 1866

[2] Zeek, P M Medical progress periarteritis nodosa and other forms of necrotizing angiitis New Eng J Med , **248** 764, 1953

[3] Rich, A R Role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy Bull Johns Hopkins Hosp , **71** 123, 1942

[4] Rich, A R Additional evidence of role of hypersensitivity in etiology of periarteritis nodosa, another case associated with sulfonamide reaction Bull Johns Hopkins Hosp , **71** 375, 1942

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A METHOD OF LENGTHENING AND REPAIRING THE PENIS IN EXSTROPHY OF THE BLADDER

FRANK HINMAN, JR

From the University of California School of Medicine, San Francisco, Calif

Four important factors in the correction of the external defects in exstrophy of the bladder in the male are 1) closure of the lower abdominal hernia, 2) removal of the mucous membrane of the bladder, 3) release of the dorsal angulation of the penis, and 4) formation of an adequate urethra with preservation of the prostatic ducts

The technique described here achieves a lengthened penis and an adequate urethra by applying the well-established principles used in the first-stage repair of hypospadias The necessary additional covering for the longer penis is obtained from a scrotal skin tube, thus adapting the principle of Wehrbein,[1] who used a similar type of tube in his two-stage method of repair of hypospadias

That a channel must be provided for the outflow of prostatic fluid was well-illustrated by the case of one patient surgically treated by an earlier method, and for whom ejaculation was always painful A perineal diverticulum finally developed, which was fixed open by suturing its edges to the perineal skin (fig 1) Subsequent ejaculation was painless

Previous methods have been successful in forming a urethra and closing the abdominal defect, but have not effected release of the dorsal penile fascia and so have not provided for lengthening of the penis H H Young[2] was able to place the urethra in an almost normal position by freeing the margins of the urethral mucosa and separating the corpora cavernosa In this technique, the abdominal closure was strengthened by flaps from the anterior rectus sheath This was not necessary, however, in the cases in the present series A further refinement was used by Mitchell and Hardin,[3] who mobilized a pedicled skin graft to close the abdominal skin defect This thick skin was not entirely suitable, however, for covering the proximal portion of the dorsum of the penis In none of the recorded techniques was release of the angulated penis achieved

TECHNIQUE

Urinary diversion has been accomplished by ureterosigmoidostomy, usually without proximal colostomy Perhaps this is not the best way, but it has been satisfactory in general An ileal conduit, or, better, a rectal bladder especially with the distal end of the sigmoid brought through the rectal sphincter, as done in our latest case, is now preferable The type of diversion used does not alter the technique of subsequent plastic repair

Read at annual meeting of the American Association of Genito Urinary Surgeons Hot Springs Va May 1-3 1957

Drs Harry M Blackfield and Gerald M Miller were active in the initial stages of development of the technique

[1] Wehrbein H L Hypospadias J Urol 50 335, 1943

[2] Young H H Exstrophy of the bladder first case in which normal bladder and urinary control have been obtained by plastic operations Surg Gynec & Obst , 74 729-737 1942

[3] Mitchell A D and Hardin C A Methods of repairing exstrophy of bladder Amer Surgeon 18 156-159 1952

described by others in cases that were caused by angiitis The history suggests that our patient became sensitized to a sulfonamide compound, gantrisin, in October 1954 and when the drug was again administered in January 1955 a hypersensitivity reaction occurred It seems unusual that the urinary bladder became the main target organ although the followup history suggests more diffuse organ involvement The apparently complete recovery of the bladder with *simple suprapubic drainage would indicate this to be the preferred treatment*

SUMMARY AND CONCLUSIONS

An unusual and apparently rare disease of the bladder is described and pathologically classified as acute necrotizing angiitis It is believed to be a hypersensitivity reaction and the evidence strongly suggests reaction to gantrisin

Complete recovery followed simple suprapubic drainage of the bladder Cystoscopic examination 17 days after operation showed the bladder had returned to normal There has been no return of bladder difficulty during a followup of 2 years and 3 months

The subject of hypersensitivity to sulfonamides is briefly discussed particularly *with reference to the production of necrotizing angiitis*

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A METHOD OF LENGTHENING AND REPAIRING THE PENIS IN EXSTROPHY OF THE BLADDER

FRANK HINMAN, JR

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Four important factors in the correction of the external defects in exstrophy of the bladder in the male are 1) closure of the lower abdominal hernia 2) removal of the mucous membrane of the bladder 3) release of the dorsal angulation of the penis and 4) formation of an adequate urethra with preservation of the prostatic ducts.

The technique described here achieves a lengthened penis and an adequate urethra by applying the well-established principles used in the first-stage repair of hypospadias. The necessary additional covering for the longer penis is obtained from a scrotal skin tube thus adapting the principle of Wehrbein[1] who used a similar type of tube in his two-stage method of repair of hypospadias.

That a channel must be provided for the outflow of prostatic fluid was well-illustrated by the case of one patient surgically treated by an earlier method and for whom ejaculation was always painful. A perineal diverticulum finally developed which was fixed open by suturing its edges to the perineal skin (fig. 1). Subsequent ejaculation was painless.

Previous methods have been successful in forming a urethra and closing the abdominal defect but have not effected release of the dorsal penile fascia and so have not provided for lengthening of the penis. H. H. Young[2] was able to place the urethra in an almost normal position by freeing the margins of the urethral mucosa and separating the corpora cavernosa. In this technique the abdominal closure was strengthened by flaps from the anterior rectus sheath. This was not necessary however in the cases in the present series. A further refinement was used by Mitchell and Hardin[3] who mobilized a pedicled skin graft to close the abdominal skin defect. This thick skin was not entirely suitable however, for covering the proximal portion of the dorsum of the penis. In none of the recorded techniques was release of the angulated penis achieved.

TECHNIQUE

Urinary diversion has been accomplished by ureterosigmoidostomy usually without proximal colostomy. Perhaps this is not the best way but it has been satisfactory in general. An ileal conduit or better a rectal bladder especially with the distal end of the sigmoid brought through the rectal sphincter as done in our latest case is now preferable. The type of diversion used does not alter the technique of subsequent plastic repair.

Read at annual meeting of the American Association of Genito-Urinary Surgeons, Hot Springs, Va., May 1-3, 1957.

Dr. Harry M. Blackfield and Gerald M. Miller were active in the initial stages of development of the technique.

[1] Wehrbein, H. L.: Hypospadias. J. Urol., 50: 335, 1943.

[2] Young, H. H.: Exstrophy of the bladder; first case in which normal bladder and urinary control have been obtained by plastic operations. Surg., Gynec. & Obst., 74: 729-737, 1942.

[3] Mitchell, A. D. and Hardin, C. A.: Methods of repairing exstrophy of bladder. Amer. Surgeon, 18: 156-159, 1952.

described by others in cases that were caused by angiitis The history suggests that our patient became sensitized to a sulfonamide compound, gantrisin, in October 1954 and when the drug was again administered in January 1955 a hypersensitivity reaction occurred It seems unusual that the urinary bladder became the main target organ although the followup history suggests more diffuse organ involvement The apparently complete recovery of the bladder with simple suprapubic drainage would indicate this to be the preferred treatment

SUMMARY AND CONCLUSIONS

An unusual and apparently rare disease of the bladder is described and pathologically classified as acute necrotizing angiitis It is believed to be a hypersensitivity reaction and the evidence strongly suggests reaction to gantrisin

Complete recovery followed simple suprapubic drainage of the bladder Cystoscopic examination 17 days after operation showed the bladder had returned to normal There has been no return of bladder difficulty during a followup of 2 years and 3 months

The subject of hypersensitivity to sulfonamides is briefly discussed particularly with reference to the production of necrotizing angiitis

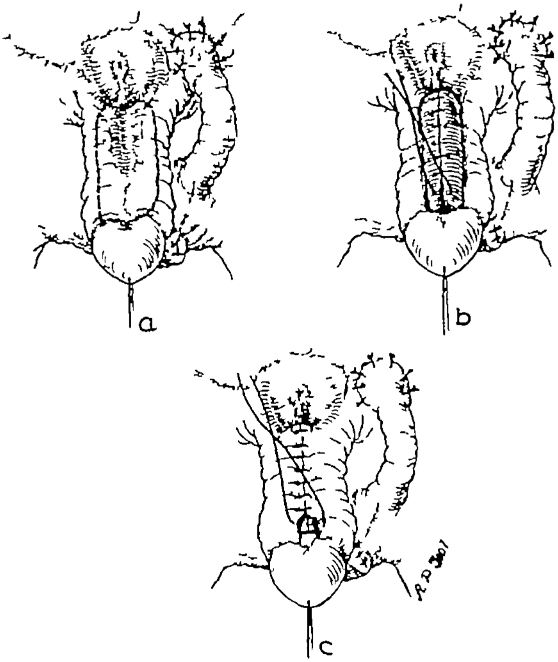

FIG 3 Second stage repair *a*, Lower end of skin tube is moved up to margin of prostatic urethra *b* Urethral tube is made by rolling dorsal skin inward *c*, Defect is covered by redundant dorsal skin

First-stage repair of epispadias is best done at the same time as the cystectomy An incision is made along the margins of the dorsal urethral mucosa, it is then carried as a circumcision around the glans (fig 2, *b*) This allows removal of the fibrous tissue at Buck's fascia (fig 2, *c*) At the same time, the dense fibrous bands (? divided suspensory ligament of the penis) holding the corpora cavernosa at the crura are cut with scissors (fig 2, *c*) to release the base of the penis These two steps lengthen the penis considerably

The ventral prepuce is split (fig 2, *d*) and moved dorsally to cover the distal portion of the penis, since the urethral mucosa proper now only reaches to just beyond the midpoint (fig 2, *e*)

A "Wehrbein" skin tube is raised from the left half of the scrotum and will be used to cover the defect produced in the third stage

Second-stage repair of the epispadias follows the first in 3 to 4 months The lower end of the skin tube is severed and attached to the margin of the suprapubic skin near the prostatic urethra (fig 3, *a*) Incisions are made along the dorsum which allow a urethral tube to be formed (fig 3, *b*) This in turn is covered by the redundant dorsal skin originally supplied by the prepuce (fig 3, *c*)

Third-stage repair of the epispadias is begun by freeing the margins of the mucous membrane of the prostatic urethra (fig 4, *a*) Division of the distal end of the skin tube allows it to be swung up and opened (fig 4, *b*) The urethral mucosa is closed by inversion with 4-0 chromic catgut sutures (fig 4, *b*) and the resulting raw surface is covered with the opened-out skin tube (fig 4, *c*)

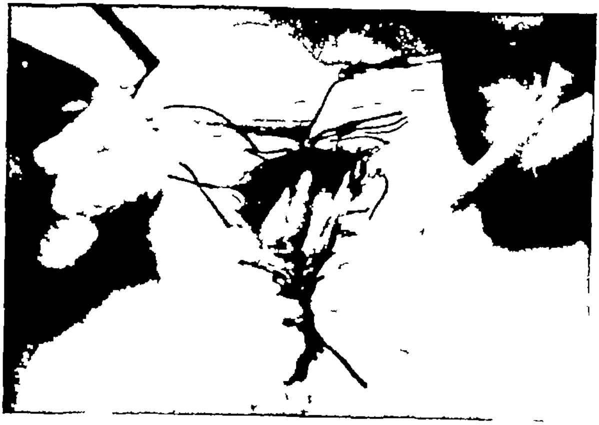

FIG 1 Result of obstruction to prostatic secretions with exstrophy of bladder Perineal fistula was required to drain prostatic fluid

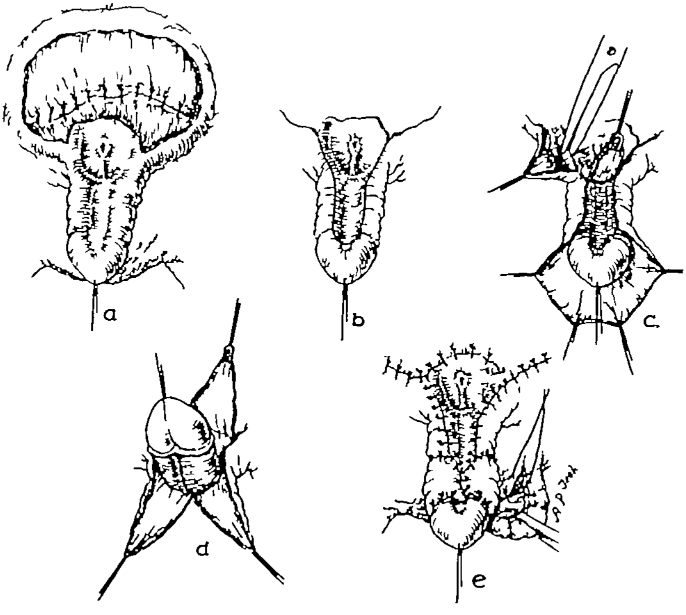

FIG 2 First stage repair *a*, Mucosa and submucosa have been removed from detrusor, which is inverted and closed by bringing abdominal fascial layers down to interpubic fascia *b*, Incisions are made on dorsum and about glans *c*, Penis is lengthened by removal of fibrous tissue at Buck's fascia and division of two portions of suspensory ligament of the penis *d*, Ventral prepuce is split *e*, Prepuce is swung around to cover distal portion of penis, while urethral mucosa proper covers proximal end Skin tube is raised from scrotum

Cystectomy has been done by excising the mucosa and submucosa from the entire detrusor, leaving a ring of mucosa around the ejaculatory ducts (fig 2, *a*) The detrusor is merely pushed down into the abdominal cavity, and the thickened, fused, fascial layers are brought down to the interpubic fascia with heavy, chromic catgut sutures The abdominal skin can usually be undermined and either moved down to join the mucous membrane of the prostatic urethra (fig 2, *e*), or closed in a Z-fashion from side to side

RESULTS

Ten boys have been operated upon by the described technique Three separate stages of repair were used in the eight completed cases In the two most recent, and so incompleted, cases, the cystectomy was combined with the first-stage repair

The increased length of the penis, which has been accomplished by dissection of the mucous membrane and its underlying fascia from the dorsum and severing the heavy, fibrous bands which attach the penis to the pubes, has been quite impressive (fig 5) It is comparable to the release of the penis obtained in the first stage of repair of hypospadias

A slight separation of the opened skin tube occurred at the base of the penis in seven cases after the third stage Two explanations have been suggested One is that the pressure dressing caused maceration and movement, the second is that the skin tube was not of sufficient length or diameter, so that tension caused the edges to heal poorly The latter is especially harmful in a field notoriously difficult to sterilize Making a wider, thicker tube, and keeping the occlusive dressings in place only six or eight hours, appear to have obviated these difficulties, especially if Aeroplast spray is used as the primary dressing

A second hazard, occurring in two cases at the second stage, was the separation of the end of the skin tube after it had been sutured next to the base of the bladder The causes here are the same as those producing skin separation at the final stage Since using a wide flap of skin for the tube, we have not observed this complication

SUMMARY AND CONCLUSIONS

A three-stage technique is described for lengthening the penis and correcting its dorsal angulation, and for constructing a prostatic and pendulous urethra in the male child with exstrophy of the bladder

At the first stage, the penis is released by raising the distal urethral mucosa and by releasing the suspensory ligaments of the penis The mobilized prepuce covers the resulting distal defect A skin tube is then raised from the scrotum

At the second operation, the distal urethra is formed by infolding the dorsal skin The skin tube is moved adjacent to the base of the penis

At the final stage, the prostatic urethra is closed and covered with the opened-out skin tube

Ten cases are reported which have been operated upon by this technique In all of them the penis has been effectively lengthened

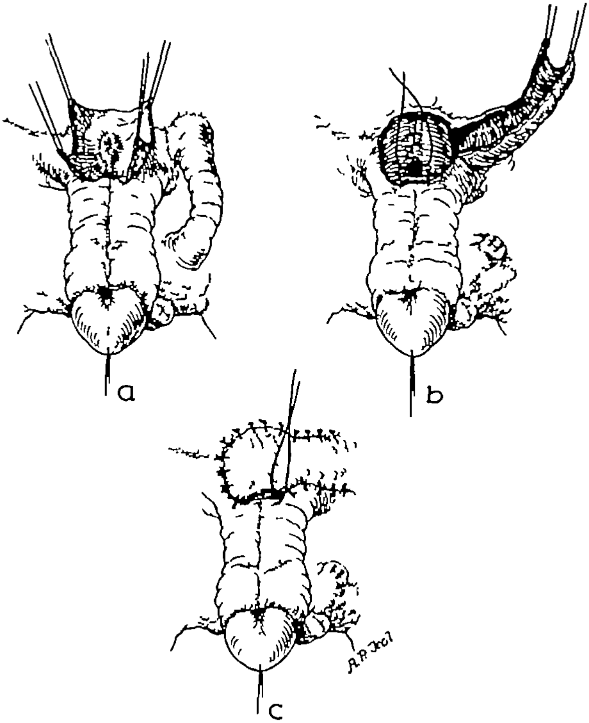

FIG 4 Third stage repair *a*, Margins of mucous membrane of prostatic urethra are incised, and *b*, closed by inversion Skin tube is freed at distal end and opened, to cover, *c*, remaining raw surface

FIG 5 Typical cosmetic result Note horizontal penis, dorsal urethra and filled in pubic defect (Case D C)

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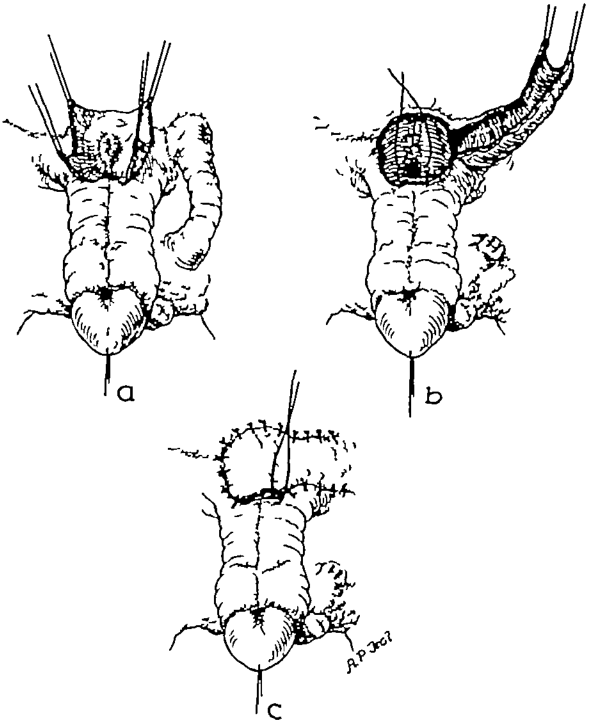

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reported 17 cases, none of them exstrophy patients They reported good continence of the urine in the modified rectal bladder, and also good control as to the bowel content, through the new anal opening Likewise Stonington and Eiseman have reported five cases with good results all in adults with bladder tumor The principle of having the rectal sphincter control both the urinary and fecal outlets was also used in 1912 by Heitz-Boyer and Hovelacque, who brought the proximal bowel segment down behind the rectal bladder In addition, they tried to bring it immediately under the anal mucosa so as to get the full benefit of the internal portion of the anal sphincter This procedure never was widely used so far as we know

Since its revival, the Gersuny procedure has been used chiefly on older individuals who required cystectomy for carcinoma of the bladder To use the procedure on the child who has many years of life expectancy requires additional consideration of the long-term possible after-effects of the procedure This is particularly true in regard to deleterious effects on the kidney function which might appear over many years of time

Considering the purely mechanical aspects of emptying function, this procedure gives the closest approximation to normal of any of the artificial methods of urinary and fecal disposal Ideally, it gives complete voluntary sphincter control It can give an acceptable voiding pattern in that the urine can be held for normal periods of time and stool likewise It eliminates entirely the need for an appliance The bowel activity pattern even if not entirely normal, will be a great improvement over any other type of colostomy The near normal location of the disposal orifices is a great convenience and a social advantage if not a medical one

We return then to the possible disadvantages of this procedure Most important would be any serious damage to the kidneys Boyce and Vest showed that isolation of the rectal segment from the fecal stream might do away with nearly all the harmful side effects which accompanied ureteral transplantation into the intact bowel They showed that the urine in such an isolated rectal bladder could be sterilized and maintained in a sterile state and that back pressure effects and electrolyte disturbances need not occur Others have reported favorable results in the use of the isolated rectum as a urinary reservoir (Kinman and associates, Smith and Hinman, Paull and Hodges)

These results seemed to us to justify trial of this procedure in the child with bladder exstrophy even though there were no known reports of long survival with this procedure Also, to bolster our determination was the fact that this operation does not bar the use of alternative procedures later on, should the result not be satisfactory

The patients selected for trial of this procedure were particularly examined for competence of the rectal sphincter The patients selected also have had essentially unimpaired upper urinary tracts before surgery The procedure is available for use after attempts at reconstruction of the bladder One of our cases was in this category having had many surgical operations for bladder reconstruction but without success The age has not been a critical point in selection One of the cases was under two years of age We see no reason for not doing this

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URETERORECTOSTOMY AND PREANAL COLOSTOMY FOR BLADDER EXSTROPHY

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The history of attempts at surgical relief of bladder exstrophy go back more than 100 years to 1851–52 when Mr Lloyd, a surgeon, and Sir John Simon attempted to divert the urine from the ureters into the rectum by establishing suture fistulas These attempts were unsuccessful and no further efforts at urinary diversion were reported until the time of Maydl about forty years later (1894) Maydl first dissected out the vesical trigone with the ureteral orifices intact, then, turning the trigone over, he implanted it into the anterior rectal wall This procedure was successful in Maydl's hands in a number of cases and inspired many variations in technique during the next fifteen years

Mauclaire, in 1895, performed experiments on animals in which he isolated the rectum, transplanted the ureters into the isolated segment, and made a proximal colostomy At this time he suggested the possibility of making a perineal colostomy or perineal anus

Within the next year or two this last suggestion was carried out by Gersuny The procedure was accomplished in two cases We have been unable to locate a report by Gersuny himself giving the details of the surgery or the results The patients apparently lived, for Gersuny's work was reported by a Dr Foges at a meeting of the Royal and Imperial Society for Physicians in Vienna This report then appeared in the WIENER KLINISCHE WOCHENSCHRIFT of 1898 The same report was copied in the CENTRALBLATT FÜR CHIRURGIE of 1899 Roughly translated the report is as follows "The rectum is separated from the sigmoid flexure and in the opening is implanted the freed up ureters together with a portion of the bladder (trigone) The divided sigmoid flexure is then drawn down through an opening in the rectouterine fold in front of the anterior rectal wall and drawn through the anal sphincter and fixed there with sutures, so that the bladder made of the separated rectal portion and the drawn down rectum made from the sigmoid flexure are both under the control of the same sphincter muscle "

A very clear drawing of this procedure appears in Frank Hinman and Henry Weyrauch's very complete review of methods of ureterointestinal implantation which appears in the transactions of this society for the year 1936 * Gersuny's name does not appear in the bibliography of this article however, and this made it very difficult to find the source of the report Bibliographical reference is under the name of Foges and so far as we are able to ascertain, no other report of this work appeared

This procedure was not further used so far as we know until revived by Drs Lowsley and Johnson a few years back (1955) About one year ago Johnson

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Read at annual meeting of the American Association of Genito Urinary Surgeons Hot Springs Va , May 1–3 1957

*Trans Am Assn Genito Urin Surg 29 15–156 1936 dominal wall and the mobilization along both the lateral and the mesenteric borders of the descending colon was continued on upward as far as necessary to get adequate length for the colon to be brought out to the perineum In one of these cases it was necessary to continue this liberation of the descending colon up to and around the splenic flexure The mesentery was found to be relatively avascular if the dissection was done far enough from the colon itself Particular attention was given to avoiding trauma to the marginal vessels along the medial aspect of the colon

After obtaining satisfactory mobilization of the descending colon a transverse perineal incision was made anterior to the anal opening and the external sphincter of the anus was identified and lifted from the internal sphincter and the rectal wall according to the general principles applied in the Belt operation for perineal prostatic exposure The prerectal space was entered both from above and below and a tunnel was formed anterior to the rectal wall An intestinal clamp was now passed upward through this tunnel from the perineum and after applying it to the mobilized colon the latter was brought down anterior to the rectum and allowed to open just anterior to the anal opening The end of the colon was now anchored to the skin of the perineum using interrupted four-0 chromic catgut sutures The redundant bowel was allowed to protrude and formed a rosette Although unsightly, these rosettes have caused no discomfort and will be removed at the time of bladder excision

We did not use drains either from the perineum or from the abdominal wounds, and have not closed the posterior peritoneal incisions either medial to or lateral to the descending colon The abdominal wall layers were closed and a mushroom catheter was inserted into the rectal "bladder" and left for a period of five days We did not splint the ureterorectal anastomoses Penicillin and streptomycin were given parenterally for about six days postoperatively

CASE REPORTS

Case 1 J J was a Negro girl, born July 27, 1953 Preoperative excretory urogram at age two years and nine months showed some dilatation in the lower portions of both ureters When three years old (July 24, 1956) the operation described above was performed At operation the ureteral dilation was confirmed, the left side being approximately eight millimeters in diameter The postoperative course was excellent, and she was discharged in excellent condition after 12 days, passing urine from the isolated rectal segment and stool from the perineal opening of the sigmoid colon In following this patient, narrowing of the perineal opening of the sigmoid colon was noted and was relieved by finger dilatation

Six months postoperatively the patient suffered an acute episode of small bowel obstruction and celiotomy was done on February 7, 1957 The obstruction was found to be due to postoperative adhesions, particularly along the mesenteric edge of the mobilized descending colon She recovered promptly following lysis of these adhesions and her postoperative course has subsequently been good Her parents state that she has control of both urine and stool and they have found that when she is dressed up in her party dress she remains dry of both operation in young children since the aftercare is not a particularly difficult problem

SURGICAL TECHNIQUE

An attempt was made to reduce the intestinal bacterial flora by administration of antimicrobial agents of the poorly absorbed type We preferred a four or five day preparation with oral sulfathaladine Enemas were given preoperatively until the enema return was clear The patient was placed in the supine position with the thighs abducted In these young children with bladder exstrophy we found that the perineal portion of the operation could be done without any other special position In this anomaly the entire perineum is displaced anteriorly and is reached easily General anesthesia was used in all cases The duration of the operation was approximately four hours In the three younger children a lower abdominal transverse incision was made just above the exstrophic bladder but in the adult patient a vertical incision was made in order to avoid an area of skin excoriation

After entering the abdomen the ureters were identified, isolated and freed from the pelvic brim distally Each ureter was then divided, the distal end ligated and the proximal end was allowed to drain freely into the peritoneal cavity while the rectal segment was being prepared The rectosigmoid was divided at or slightly below the level of the promontory of the sacrum between noncrushing (Dennis) intestinal clamps A small opening was then made in the distal segment and a solution of 1 gm neomycin in 500 cc of saline was used, to further cleanse this segment After this we had no hesitation in removing the previously applied clamp to do the ureterorectal anastomosis through the open bowel lumen Mucosa-to-mucosa anastomosis was thus done with the ureters pulled through small lateral incisions in the posterior wall of the rectum The ureters were prepared by cutting the end obliquely and extending the incision for a short way to further enlarge the circumference of the now elliptical ureteral end Five-0 chromic catgut suture was used to approximate the full thickness of ureteral wall and the rectal mucosa In general, a single layer anastomosis was used, although on occasion a few supporting sutures were taken between the serosa of the rectosigmoid and the areolar tissue around the ureter The proximal end of the rectum was closed using two rows of number four-0 chromic catgut suture reinforced with a few silk sutures

Attention was then directed toward freeing the attachments of the descending colon in order that an adequate length could be brought through to the perineum The inferior mesenteric artery was isolated a short way from its origin from the aorta and a bulldog clamp was applied here If the colon did not appear to become ischemic following the application of the bulldog clamp the inferior mesenteric artery was divided and ligated In none of these cases was there any indication of ischemia after ligation and division of the inferior mesenteric artery In some of the cases the inferior mesenteric vein appeared to limit mobility and it likewise was sectioned after a temporary occlusion with the bulldog clamp

The lateral attachments of the colon were severed from the left lateral abwith a minimum of difficulty in stool control He now reports that within recent weeks he has been able to discriminate between stool and gas in the sigmoid and he claims considerable skill in control of the latter

Case 3 R G was a white girl born on May 10, 1955 When first seen, the advisability of diversion procedures to the colon was questioned because it seemed that this child had subnormal anal sphincter activity On following this patient over several months it seemed that the anal sphincter activity improved somewhat and she was finally considered for the above procedure Excretory urogram done preoperatively, at age four months, showed a normal upper urinary tract On September 18, 1956, at 16 months of age, she was operated upon according to the technique described The postoperative recovery was excellent and she was discharged 10 days following operation Postoperatively her general condition has been excellent, with no clinical evidence of pyelonephritis Because of her age (still less than two years) it is difficult to determine if there is adequate control over the urine and stool, however, the mother feels that there has been some progress in recent attempts at toilet training Urinalysis done five months postoperatively discloses 0–1 white cell per high power field and the urine is grossly clear except for mucus There is no residual urine in the rectal bladder The stool has been formed or soft and again control is difficult to determine An excretory urogram made two months postoperatively showed a normal upper urinary tract Blood chemistry studies five months postoperatively showed sodium 145, potassium 5.2, chloride 110, Co_2 23, and nonprotein nitrogen 23 Seven months postoperatively the blood chemistries were again normal with sodium 144, potassium 4 4, chloride 109, Co_2 23, nonprotein nitrogen 18

Case 4 S E, a white boy born on October 20, 1954, was noted by his parents to have unexplained fevers which perhaps were related to ascending urinary tract infection Excretory urogram at age of two years showed mild dilatation of the right ureter The parents noted constipation in the patient and a barium enema was stated to show a redundant colon He entered the hospital in June 1955, at age of eight months because of the development of an incarcerated inguinal hernia Abdominal exploration at this time disclosed a gangrenous small intestine which was resected A few weeks following this procedure both left and right inguinal hernias were repaired through inguinal incisions The operation for urinary diversion described above was performed November 27, 1956, at the age of 25 months The postoperative course was excellent, the patient being discharged fifteen days postoperatively passing urine and stool from the separate openings Two weeks postoperatively the chemistry values were sodium 137, potassium 4 7, chloride 109, Co_2 25, nonprotein nitrogen 25 Two and one-half months postoperatively the chemistry levels were sodium 142, potassium 4 9, chloride 117, Co_2 19, nonprotein nitrogen 25 When repeated again four and one-half months after operation, values were obtained of sodium 144, potassium 5 0, chloride 112, Co_2 23, nonprotein nitrogen 22 The extent of control over urine and stool is difficult to assess in this young patient, now two and one-half years old, but the mother feels that both urine and stool control are probably present The residual urine is less than 20 cc and the urine is grossly clear with only an occasional white blood cell seen microscopically The general condition of stool and urine for periods up to three hours Urine culture from the rectal segment on January 11, 1957 disclosed mixed bacterial growth, including E coli, Proteus, and Streptococcus Grossly the urine is hazy with mucus shreds, microscopically only a few white blood cells and a few bacteria are seen

After strenuous crying when seen in the clinic the patient was noted to have no residual urine in the rectal segment There has been no indication of difficulty in passing the stool Excretory urogram done two months postoperatively shows a normal upper urinary tract which actually appears improved over the preoperative films Electrolyte studies done five months postoperatively show sodium 140 meq/L, potassium 4 5 meq/L, chloride 113 meq/L, Co_2 18 meq/L, and nonprotein nitrogen 25 mg /100 ml Repeat studies done eight months postoperatively revealed chloride 117 and Co_2 19 Her general condition has been excellent She has had no clinical evidence of pyelonephritis

Case 2 K W was a white male senior in high school whose exstrophy of the urinary bladder had been treated by attempted closure at the age of four years Numerous unsuccessful attempts were made subsequently to close fistulas No apparent urinary sphincter activity was observed on preoperative cystourethroscopic examination This boy was quite uncomfortable due to urinary drainage to the anterior abdominal wall where there was moderate excoriation of the skin He was attending a special school and wearing diapers On November 4, 1956, at age of 19 years, the previously described operation was performed Sulfathaladine and neomycin were used for preoperative bowel preparation The operative position was that used for synchronous combined abdominoperineal resection of the rectum, and gave very excellent exposure both abdominally and perineally A vertical left paramedian incision was used in this case to avoid the excoriated area around the fistulas Surgery was uneventful The postoperative hospital course was excellent He was discharged 11 days postoperatively passing urine and stool from the separate openings He likewise has had mild stricture formation at the perineal sigmoid opening which he has controlled by self dilatation Urine culture three months postoperatively revealed the presence of Proteus and enterococcus A "rectometric" study was done postoperatively and disclosed that the maximum pressure within the rectal bladder was 25 mm of mercury and the capacity was 200 cc An excretory urogram made two months postoperatively showed dilatation of the lower left ureter but a subsequent urogram, five months postoperatively, showed a normal upper urinary tract Blood chemistry studies five months postoperatively showed sodium 145, potassium 5 1, chloride 111, Co_2 24, nonprotein nitrogen 27 This patient's general health prior to the operation performed here was fairly good, although he is very thin for his body build Recently he has gained a few pounds in weight and his general health has been good with no clinical evidence of pyelonephritis His urine control has been excellent for which he is very grateful Residual urine was 5 cc The control of stool was not good for several months as he lost both formed and liquid stool without warning in spite of the fact that digital examination of the sigmoid opening indicated a fairly vigorous voluntary sphincter muscle action upon this segment His control of the stool has improved a great deal in recent months and, although still not perfect, he is working every day with a minimum of difficulty in stool control He now reports that within recent weeks he has been able to discriminate between stool and gas in the sigmoid and he claims considerable skill in control of the latter

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Case 4 S E, a white boy born on October 20, 1954, was noted by his parents to have unexplained fevers which perhaps were related to ascending urinary tract infection Excretory urogram at age of two years showed mild dilatation of the right ureter The parents noted constipation in the patient and a barium enema was stated to show a redundant colon He entered the hospital in June 1955, at age of eight months because of the development of an incarcerated inguinal hernia Abdominal exploration at this time disclosed a gangrenous small intestine which was resected A few weeks following this procedure both left and right inguinal hernias were repaired through inguinal incisions The operation for urinary diversion described above was performed November 27, 1956, at the age of 25 months The postoperative course was excellent, the patient being discharged fifteen days postoperatively passing urine and stool from the separate openings Two weeks postoperatively the chemistry values were sodium 137, potassium 4 7, chloride 109, Co_2 25, nonprotein nitrogen 25 Two and one-half months postoperatively the chemistry levels were sodium 142, potassium 4 9, chloride 117, Co_2 19, nonprotein nitrogen 25 When repeated again four and one-half months after operation, values were obtained of sodium 144, potassium 5 0, chloride 112, Co_2 23, nonprotein nitrogen 22 The extent of control over urine and stool is difficult to assess in this young patient, now two and one-half years old, but the mother feels that both urine and stool control are probably present The residual urine is less than 20 cc and the urine is grossly clear with only an occasional white blood cell seen microscopically The general condition of this patient has been most excellent The mother states that he has been considerably improved compared to his preoperative status He has had no further unexplained elevation of temperature

DISCUSSION

In all of the cases this operation has resulted in a satisfactory urinary reservoir under sphincter control This has been accomplished without serious deleterious effects on the upper urinary tract in any case These findings are in accord with those of practically all authors who have previously reported the use of the isolated rectum as a urinary reservoir, when the procedure has been done as a primary procedure with a previously normal upper urinary tract High pressures do not develop in the isolated rectal bladder as they do in the normal rectum as a result of peristaltic waves or of defecation efforts Pressure studies of such rectal bladders done by Smith and Hinman and Paull and Hodges have brought out this point of relatively low pressure in the rectum when used as a urinary reservoir This helps explain why no kidney damage is reported by the authors using this procedure There has been no instance of pyelonephritis in any of our cases, and this too is in accord with the experience of others The urine in our cases has not been sterile but the cell counts are low and any infection present has not seemed to involve the kidneys but rather to remain localized in the lower tract

None of our patients has had symptoms of electrolyte imbalance There has been no anorexia or any other premonitory symptom of acidosis However, in two cases, electrolyte determinations have shown moderate variation from normal on one or more determinations following surgery In these patients, there have been found chloride levels of 117 meq/L with CO_2 levels of 19 meq/L At the time of these findings, the patients were in apparent perfect health and were feeling well In one case, these values, two months later, were chloride, 112 mEq and CO_2 23 mEq , but in the second case, they have not returned entirely to normal We will continue to watch the electrolyte levels in these patients We do not anticipate serious clinical effects since the area of bowel mucosa exposed to the urine is so much smaller than that in conventional ureterosigmoidostomy into the intact bowel It has been definitely shown that some electrolyte reabsorption does occur from the isolated rectal bladder (Boyce 1951, Parsons and associates 1952) The good kidney function which this procedure permits will help offset the reabsorption that occurs and we hope that it will prevent any serious consequences Dr Creevy's experience with isolation of the rectum some time after ureterosigmoidostomy is not a directly comparable situation, but it, too, affirms the fact that there is significant reabsorption from the distal colon and rectum Although the rectum may reabsorb less actively than the higher portions of the bowel, such as the ileum, still the urine is held in contact with the rectal wall for a matter of hours as compared to uretero-ileostomy in which emptying is usually quite rapid

The control of the stool has been difficult to determine in the three younger patients of our group The bowel movements are periodic in the children at intervals of one to several times a day However, because of the age of the children, it cannot be said at this time that these are entirely voluntary The one older patient of this group has had a delay of several months in securing satisfactory control of stool and gas His early difficulty seemed to be due more to incomplete sensation of stool or gas being present in the terminal sigmoid rather than due to a defect of voluntary muscle strength Perhaps a new system of co-ordination must be set up to insure adequate sustained external sphincter tone after this operation

Difficulties with stool control have not been mentioned in the reports of others using this procedure The fact is that only the external sphincter is working on the bowel segment containing stool The internal rectal sphincter is an intrinsic part of the rectal wall and does not act on the sigmoid colostomy after the procedure described here The operation described by Heitz-Boyer and Hovelacque was designed to make use of the internal as well as the external sphincter but its use has not been reported recently

SUMMARY

Four patients with exstrophy of the bladder have been operated upon by a method originally used by Gersuny in 1895 The early (nine to six months) functional results have been quite encouraging Harmful effects on the upper urinary tract have not been noted Mild subclinical acidosis has been found by blood chemistry studies in two cases This effect will be followed closely for proper evaluation of the use of this procedure in young children

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ILEOCYSTOPLASTY FOR BLADDER ENLARGEMENT

LOUIS M ORR, MILES W THOMLEY AND JAMES L CAMPBELL

A 63-year-old white man first consulted an urologist elsewhere in March 1948, complaining of frequency and urgency of urination of about six years' duration with marked exacerbation a few days before examination On the initial examination the prostate was said to be somewhat enlarged and was considered benign He was placed on catheter drainage and received penicillin Subsequent cystoscopy six days later revealed an acutely inflamed mucosa with moderate intraurethral protrusion of the lateral lobes of the prostate The bladder was said to be markedly contracted, the true capacity, however, was unknown Eight days later the patient stated that tubercle bacilli were found in his urine A transurethral prostatic resection was later performed The removed prostatic tissue was reported as negative for evidence of tuberculous involvement For the next three years the patient had intermittent return of symptoms and was treated with streptomycin, chloromycetin and sulamyd at different times with some relief, but upon cessation of therapy his symptoms returned The bladder capacity on June 15, 1951 was said to be 7½ ounces and at this time he was free of pain and subjective symptoms

The patient came under our observation in June 1956 He was complaining of marked frequency, burning and great urgency of urination, both day and night, and a feeling of weight in the suprapubic region, especially when lying down With this present attack of frequency there was considerable nausea for the first time since 1951 He stated that he underwent a left nephrectomy in 1915 for a football injury in 1913 An intravenous urogram revealed a normal right upper tract and a small bladder Cystoscopy under local anesthesia revealed an extremely sensitive bladder with a residual of 1 ounce and a preliminary diagnosis of interstitial cystitis was made The prostate was of normal size and consistency and felt benign on rectal examination

On July 8, 1956 the patient was admitted to the hospital where investigation revealed essentially normal urine with an occasional white blood cell, normal blood studies and a roentgenogram of the chest revealed calcifications in the right apex which were interpreted as healed tuberculosis On July 9, 1956 a cystoscopy under spinal anesthesia revealed the bladder mucosa to be typical of interstitial cystitis The bladder could not be dilated to contain more than 100 cc fluid Two small nonretention diverticula were noted in the posterolateral aspect of the bladder The lateral prostatic lobes were slightly enlarged A culture of the urine from the bladder and right kidney was positive for Pseudomonas aeruginosa, which was found to be sensitive to polymyxin No acid fast organisms could be demonstrated

The decision was made to attempt to relieve the patient's very severe urinary distress by enlarging the bladder capacity by ileocystoplasty On July 23, 1956 the abdomen was opened through a right lower paramedian incision A segment

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Read at annual meeting of the American Association of Genito Urinary Surgeons Hot Springs, Va , May 1-3 1957 of terminal ileum measuring approximately 18 cm in length was isolated divided from the remaining bowel, as was the attached mesentery down to the base, and then closed with a Parker-Kerr stitch reinforced with interrupted No 4-0 silk sutures The small bowel was then reanastomosed with a two layer closed anastomosis The bladder was then identified and found to present a very small surface The peritoneum over the midportion of the bladder was sutured to the posterior wall of the isolated segment A two layer continuous anastomosis was then made between the bladder wall and the segment of ileum on its antimesenteric border The opening between the bladder and ileum was made approximately 4 cm in length The defect in the mesentery left by the removed segment was closed to prevent herniation The lower abdomen was drained through a stab wound A No 22 Foley catheter was placed in the bladder

His postoperative course was generally very satisfactory There was minimal drainage from the wound and on the seventh day all sutures and the drain were removed On the sixteenth day the urethral catheter was removed and by the nineteenth day the patient was voiding comfortably and without difficulty, retaining urine up to two hours

On his first postoperative visit to the office he reported the interval between voiding to be as long as five hours with nocturia of two to three times The residual was 2 ounces

On September 10, 1956 a cystogram revealed a saccular type defect filled with contrast medium above the bladder and extending toward the right On September 24, 1956 he was again seen and at that time the urine contained 10-15 white blood cells the patient had no complaints a No 24 sound passed with ease and the residual bladder urine was 2½ ounces On December 3, 1956 he had nocturia one time and a residual of 3 ounces On February 7, 1957 a cystogram revealed the ileal attachment to have increased in size and it appeared in the shape of a sausage On March 27, 1957 the patient stated he voided only once at night, was extremely happy with the result The cystogram (fig 1, A) showed good filling of the bladder and partial filling of the ileal anastomosis A

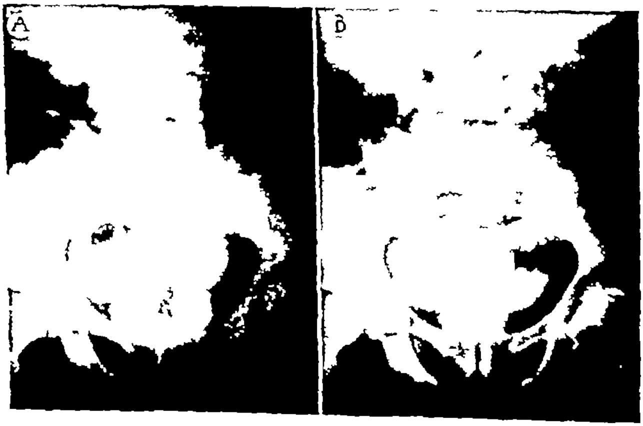

FIG 1

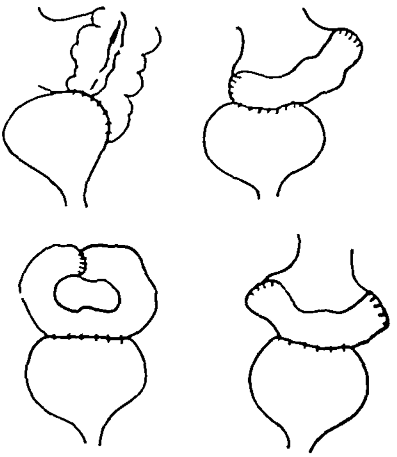

FIG 2

voiding cystogram (fig 1, *B*) showed retention of a considerable amount of the injected material and the residual urine was 6 ounces on April 1, 1957

HISTORICAL NOTES

The first operation (ileocystoplasty) was performed by von Mikulicz in 1898 Shoemaker,[1] in 1909, with the idea in mind of putting a tuberculous bladder at rest, implanted the sole remaining ureter in a loop of ileum, the lower end of which was brought out through the abdominal wall When the bladder was healed, the ileum was detached from the abdominal wall and anastomosed to the bladder During the next twenty years numerous reports of cases appeared in the Spanish, French, Belgian and British literature, where some portion of the alimentary tract was joined to the bladder Segments of the ileum, with one end closed or both ends closed, and segments of the colon and cecum were anastomosed to the bladder in various ways and fashions Scheele in 1941, anastomosed the center of an isolated loop of ileum to the bladder and then joined the ends of the loop together, producing what came to be known as a *ringplastik*

Couvelaire, in 1950, was actually the first to advocate ileocystoplasty as a suitable procedure for enlarging the healed tuberculous bladder

Jacobs[2] made a flat patch of the ileal segment by dividing the graft and then anastomosing one to the other (fig 2) This flat patch was then anastomosed to the sagittally opened bladder, the idea being to maintain the enlarged bladder in the form of a sphere Jacobs states that "the use of the terminal ileum to increase the capacity of contracted bladder is feasible and appears to be a reasonable procedure when conservative measures fail to improve capacity The optimum technique, however, has not as yet been determined and the operation is not without its hazards "

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[1] Shoemaker (1909) quoted by Hinman, F and Weyrauch, H M Trans Amer Asso Genito Urin Surg , 29 15, 1936

[2] Jacobs, Arthur Ileocystoplasty *Glascow Med J* *36* 130-135 1955

Pyrah and Raper,[3] in 1955, carefully reviewed the literature, reciting three cases and described the various surgical methods employed

In Cibert's[4] article regarding anatomic and physiopathologic factors influencing technique and indications of ileocystoplasty, he mentions that the detrusor, instead of forming an extensible cupola above the trigone, has become a rigid ceiling There the vesical cavity is composed almost entirely of the trigone Instead of anastomosing the isolated ileal loop to a simple linear opening in the bladder dome, a preliminary resection of the remaining detrusor is performed, thereby avoiding the most diseased portion of the bladder in order to prevent retraction of the lumen of the anastomosis Ileocystoplasty appears to reverse the threat of renal destruction due to increased intravesical and intraureteral pressure, by diverting the increased tension to the intestinal graft

COMMENT

Ileocystoplasty is a surgical procedure of major proportions The act of urination is likely to be somewhat abnormal during the first weeks after operation and interrupted voiding impulses are not unusual A sensation of fullness in the lower abdomen may be present Some surgeons claim that manual pressure above the pubes may assist in emptying the bladder

What is actually accomplished by the operation is to produce an artificial diverticulum which allows for greater bladder capacity This type of diverticulum does differ from the so-called acquired or true diverticulum in that the ileal loop addition does have modest contractile powers, possibly assisting in emptying the bladder It also differs in that it has a wide stoma into the bladder, which makes for better emptying of the sac The fact remains, however that the addition of the diverticulum does mean the creation of residual urine, of greater or lesser degree, the consequences of which would appear to be no different from a residuum created by any other means In the patient here discussed the residual urine has been increasing since the time of operation from two to seven ounces, and it is quite possible that the residuum may in time increase due to the positive pressure exerted by the filled bladder upon the walls of the loop Little mention is made of this sequella in the literature

Consideration must also be given to the quality of the urine after ileocystoplasty as mucus, secreted by the loop mucosa, may occur in such degree as to cause annoyance Such has not been a problem in our patient

It has recently been shown in animal experimentation by Shoemaker[5] and his group that if the mucosa is removed from the ileal loop the problem of mucus in the urine will be eliminated The use of a seromuscular ileal graft to the bladder of animals, as described by Shoemaker, may stimulate its use in the human As to how much such a graft can increase the size of the small contracted bladder is debatable, as the posterior surface of such a bladder offers not too great an area for a large sized patch considering that it is much more hazardous to anastomose a single layer of the ileum to the bladder wall than the two layers as is the case with the ileal loop Failure of the anastomosis will result in leakage of urine and possible fatality to the patient

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[3] Pyrah L N and Raper F P Some uses of an isolated loop of ileum in genito urinary surgery Brit J Surg 42 337 1955

[4] Cibert J Durand L Foret J R and Solar A Small bladder in urinary tuberculosis Anatomic and physiopathologic factors influencing technic and indications of ileocystoplasty J d urol 60 125 1954

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Ileocystoplasty is a procedure which offers great possibilities for the relief of the suffering associated with a contracted bladder, where all other conservative procedures have failed

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ELECTROLYTE ABSORPTION FROM FOWL'S CLOACA: RESISTANCE TO HYPERCHLOREMIC ACIDOSIS

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Although there has been extensive investigation of reabsorptive acidosis after operative diversion of the urine to the bowel, little attention has been directed to those factors which prevent the development of this condition in animals with a cloaca.[1] Since an additional approach might help to elucidate this postoperative complication, we have made studies of the absorption of electrolytes from the fowl's cloaca, and compared them with similar observations on the rectosigmoid of dogs and humans.

EXPERIMENTAL METHOD

In our experiments with cloacal absorption Rhode Island Red hens weighing 2.2 to 3.4 kg. were used.* With the birds under ether anesthesia 10 ml. of the test solutions was injected into the cloaca. Radioactive sodium or iodine† served as tracer elements and 0.5 ml. of 0.8 per cent solution of indigo carmine was added to each instillation. Escape of fluid was prevented by closing the anus with a purse-string suture. Coloring the fluid with indigo carmine served two purposes—it facilitated detection of the slightest leakage and at autopsy it revealed the levels reached by the instilled solution in the cloaca, oviduct, ureters and colon by staining of mucosal surfaces.

The rate and amount of absorption of electrolytes in the circulating blood were determined by measuring the uptake in 1 ml. samples of blood withdrawn from the jugular vein at intervals of from five to thirty minutes for four or five hours after instillation. At this time autopsy was performed. Observations were made of the extent of local distribution of the fluid as shown by mucosal staining. In several animals the fluid remaining in the cloaca was tested for residual radioactivity. In all the animals in which I^{131} was used, the thyroid was removed and its content of radioactive material was measured.

The amount of isotope in the blood samples and the thyroid gland was measured with a Tracerlab scintillation counter. By comparison with a standard solution the counts per minute were converted into microcuries of isotope. The

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Read at annual meeting of the American Association of Genito-Urinary Surgeons, Hot Springs, Va., May 1-3, 1957.

[1] Weyrauch, H. M. and Hinman, F.: An experimental study of uretero intestinal implantation. III. The significance of ureterocloacal re implantation in the chicken. Surg., Gynec. & Obst., 70: 170–177, 1940.

* By making blood serum determinations of chloride and creatinine in several hens we found that the normal values in the fowl coincide with those in the human. The chloride in the hens ranged from 88 to 111 meq/L., and the creatinine from 0.3 to 1.4 mg. per cent.

† Absorption of chlorine and iodine from the gastro intestinal tract, their diffusion (except in the thyroid gland) and excretion are similar.[2]

[2] Hanzlik, P. J.: Quantitative studies on the gastro-intestinal absorption of drugs. II. The absorption of sodium iodine. J. Pharmacol., 3: 387–421, 1912.

amount in the total circulating blood was calculated by using 7 3 per cent of the animal's total weight as the weight of the total blood volume *

Total transcloacal absorption was determined by adding the amount of isotope in the circulating blood to that in the extravascular tissue spaces, and to that contained in the thyroid in the iodine experiments †

Series 1 In an initial series of 20 hens absorption of iodine and chlorine in various concentrations of fluid was observed The following solutions, each containing 250 microcuries of isotope, were instilled in the cloaca of four groups of five hens each

A) I^{131} in a hypotonic solution (less than 0 1 per cent) of NaI yielded a mean of 7 5 per cent absorbed (fig 1, *A*)

B) I^{131} in an isotonic solution (0 9 per cent) of NaI yielded a mean of 5 6 per cent absorbed (fig 1, *B*) In one of the hens 92 per cent of residual isotope was recovered from the cloaca

C) I^{131} in a hypertonic solution (2 per cent) of NaI yielded a mean of 6 7 per cent absorbed (fig 1, *C*)

D) Na^{24} in an isotonic solution (0 9 per cent) of NaCl yielded a mean of 10 7 per cent absorbed (fig 1, *D*) In two hens 91 and 88 per cent of residual isotope was recovered from the cloaca

Figure 2, *A* demonstrates the mean absorption of all electrolytes placed in the cloaca in various carriers The absorption rates, ranging from 5 6 per cent to 10 7 per cent, showed little difference between the various concentrations of fluid

As concerns the rate of absorption, within five minutes after instilling the isotope there were measurable amounts of radioactivity in the blood obtained from the jugular vein In most of the birds, maximum absorption was reached one and one-half to two and one-half hours after cloacal instillation Thereafter the blood levels remained nearly constant Apparently by this time equilibrium

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* This percentage was arrived at by calculating the blood volume in four hens using the dilution method of radioactive iodinated serum albumin This percentage closely coincides with values previously reported for chickens by dye dilution and diphtheria antitoxoid methods [3-5]

† It can be assumed that the chicken has sodium and chloride (iodine) spaces similar to that in the dog, or human, where they have been carefully studied and found to approximate 28 per cent of the total body mass [6, 7] Given the isotope content in the circulating blood, the blood being 7 3 per cent of the chicken's body weight, approximately four times this amount is the total tissue space content of sodium Similarly four times the blood amount plus the thyroid content would be the total tissue space for iodine It is confirmatory that in the three hens in which residual isotope was measured in the cloaca at the termination of the experiment, 88 per cent, 91 per cent, and 92 per cent of the isotope was found unabsorbed

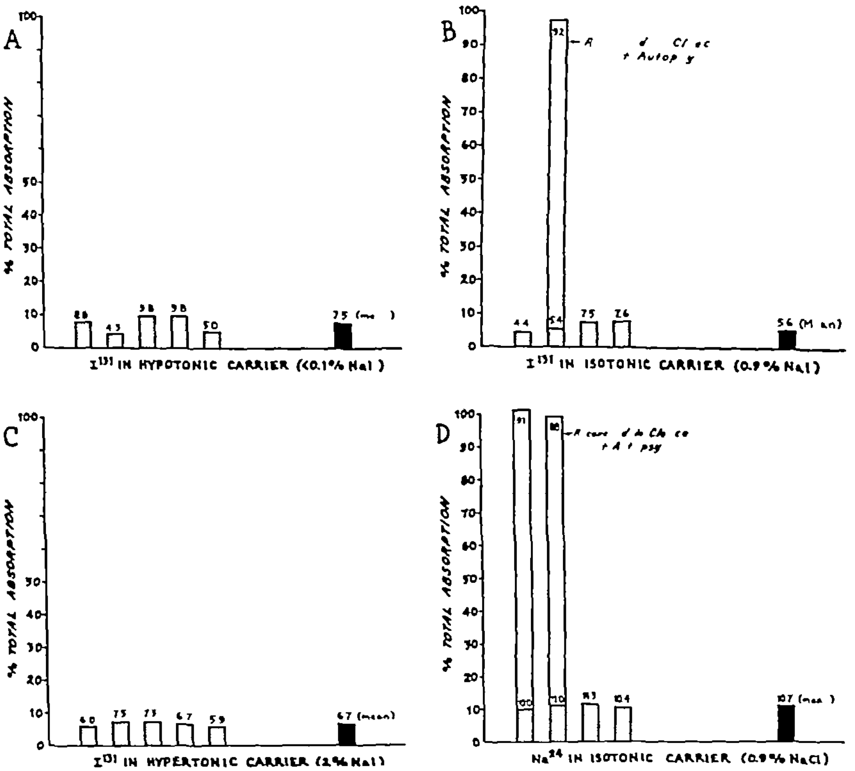
[3] Erickson, J R , McCormick, J B and Seed, L An improved method for the determination of blood volume using radio active iodinated human serum albumen Science, **118** 595–696, 1953

[4] Pino, J A , Weiss, H S , Strukie, P O and De Falco, R J Blood volume determinations in the fowl using diphtheria antitoxoid Proc Ninth World's Poul Cong , **3** 102, 1951

[5] Newell, G W and Shaffner, C S Blood volume determinations in chickens Poult Sci , **29** 78–87, 1950

[6] Winkler, A W , Elkington, J R and Eisenman, A J Comparison of sulfocyanote with radio active chloride and sodium in the measurement of extracellular fluid Am J Physiol , **139** 239–246, 1943

[7] Gamble, J L and Robertson, J S Volume of distribution of radio active chloride in dogs comparison with sodium bromide, and insulin spores Am J Physiol , **171** 659–667, 1952



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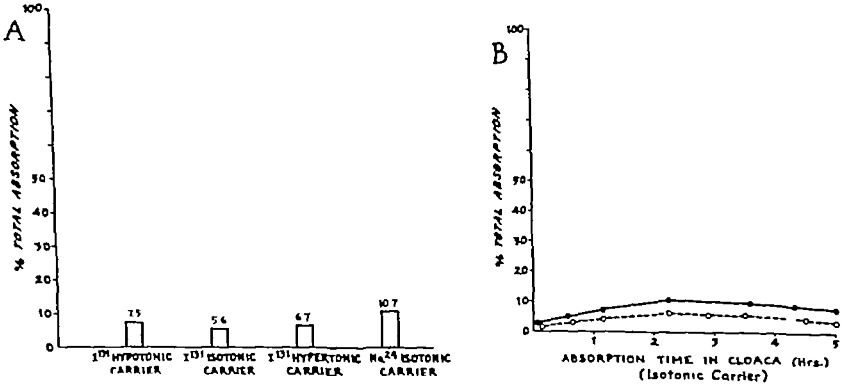

Fig 2 *A*, comparison of mean absorption of four isotope solutions from cloaca *B*, comparative rates of absorption of I^{131} and Na^{24} from cloaca of fowl ——●——●——● Na^{24}, ——○——○——○—— I^{131}

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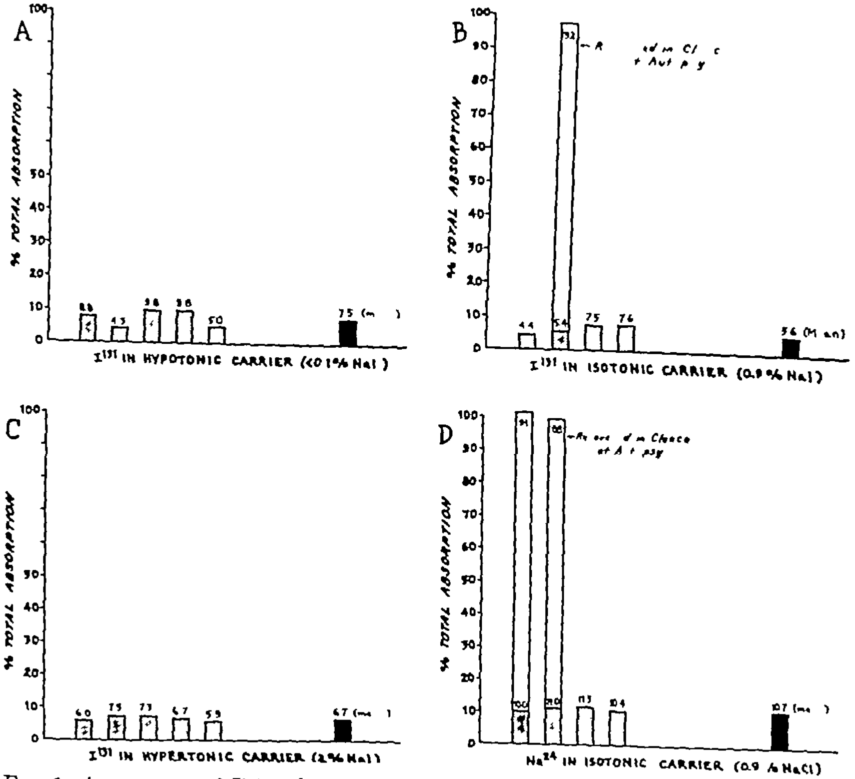

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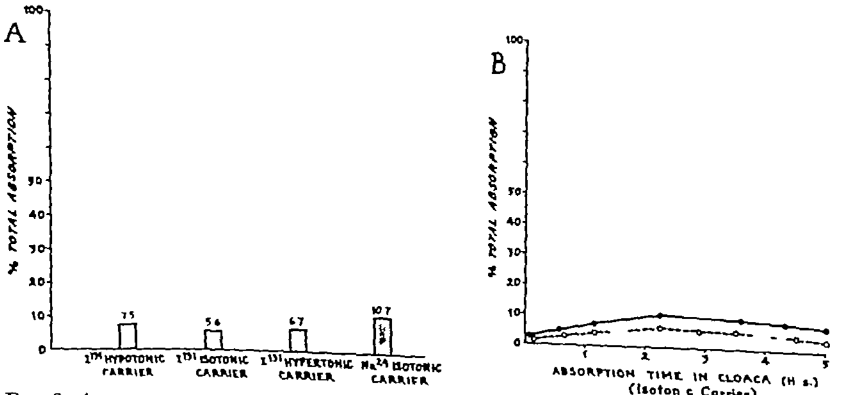

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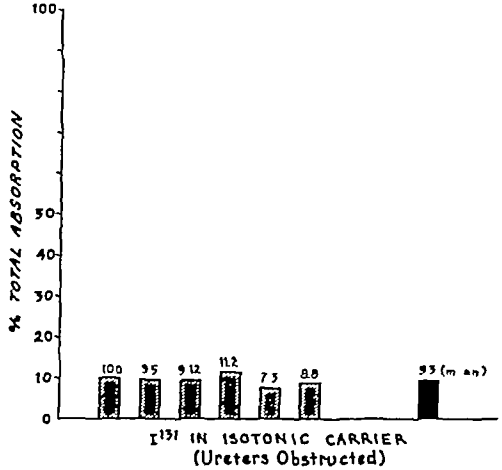

FIG 3 Amount of I^{131} in isotonic solution absorbed from cloaca of six hens with ureters completely obstructed

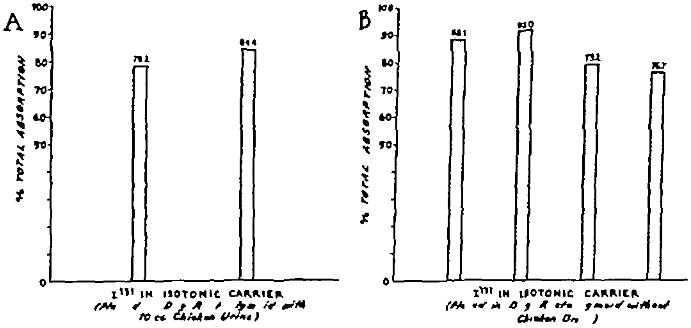

FIG 4 *A*, amount of I^{131} in isotonic solution and chicken urine absorbed from recto sigmoid of two dogs *B*, amount of I^{131} in isotonic solution absorbed from rectosigmoid of four dogs

was established between cloacal absorption, tissue space distribution, and urinary excretion of the tagged electrolyte back into the sealed cloaca By this time, too, in the I^{131} experiments, saturation of the thyroid with the iodide ion was apparently complete The rate of absorption of chlorine and iodine in the two isotonic groups is shown in figure 2, *B* It will be noted that the curve of absorption of these two electrolytes is similar

Series 2 A second series of experiments was performed to rule out the possibility that following absorption the hen rapidly excretes electrolytes back into the cloaca Such a phenomenon would mask greater absorption rates than those indicated by the previous experiments

In six hens both ureters were ligated and divided to prevent urine from entering the cloaca during the absorption studies Following this procedure cloacal absorption of I^{131} in isotonic NaI carrier was determined, as in series 1 Figure 3 shows the results in these animals

Series 3 In contrast to the low absorptive capacity of the cloaca shown in these studies, previous experiments have shown that almost all sodium and

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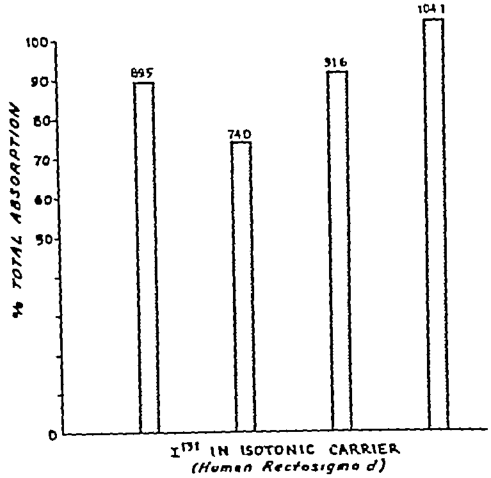

FIG 5 Amount of I^{131} in isotonic solution absorbed from rectosigmoid of four human subjects

iodine are absorbed from the rectosigmoid of dogs Rosenberg[5] demonstrated this in animals both with normal electrolyte balance and with hyperchloremic acidosis Maximal blood levels of tagged electrolytes were attained three to four hours after rectal instillation Thereafter less than 10 per cent could be recovered from the stool In order to correlate this work under similar experimental conditions, we made additional studies in dogs In two dogs, chicken urine was added to an electrolyte solution placed in the rectosigmoid This was done to ascertain whether bird's urine might contain a substance which inhibits electrolyte absorption In these animals weighing 7 8 and 8 4 kg , one millicurie of I^{131} in 100 ml of isotonic NaI was mixed with 8 5 ml of chicken urine obtained by ureteral catheterization and placed into the rectosigmoid The anal orifice was occluded by suture, and urine and blood specimens collected at intervals of 15 minutes for four hours Figure 4, *A* shows the high amounts of iodine absorbed

Series 4 In an additional four dogs (weighing 7 3, 5 4, 6 4, and 6 3 kg) the experiment performed in series 3 was repeated without the addition of chicken urine to the test solution The total absorption of the rectally placed isotope is shown in figure 4, *B* It is not significantly different from that in the animals in which chicken urine was added

Series 5 Finally, for purposes of comparison determinations were made of electrolyte absorption from the rectosigmoid of four human subjects One hour after a cleansing saline enema, 100 ml of isotonic NaI containing 300 to 358 microcuries of I^{131} was instilled 12 cm from the anal orifice as a retention solution Urine and blood were collected every 30 minutes for four hours At the conclusion of the study, radioactivity of the thyroid and rectosigmoid regions was measured Figure 5 indicates almost complete total absorption of iodine in the four patients

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[5] Rosenberg M L The physiology of hyperchloremic acidosis following uretero sigmoidostomy A study of urinary reabsorption with radio active isotopes J Urol , 70 569-580 1953

By measuring over the rectosigmoid with the scintillation counter in the first two patients, amounts of radiation above the levels elsewhere in the body (except over the thyroid) were found to be negligible In the remaining two patients, examination of feces obtained by enema showed less than 2 per cent and 3 per cent of the isotope in the rectosigmoid at the conclusion of the study

ANCILLARY OBSERVATIONS

In addition to studies of electrolyte reabsorption, other factors which might prevent reabsorptive acidosis in the fowl were investigated

Rate of cloacal emptying Hens remain erect whether awake or asleep, and empty their cloacas four or five times an hour, night and day Since our experiments were conducted with fluid retained in the cloaca for up to five hours, frequent cloacal emptying is obviously not a factor in preventing reabsorptive acidosis

Cloacal reflux-resisting factors in the fowl To study reflux 40 ml of a thin barium mixture was introduced into the cloaca of six hens and the anal orifice sealed with a purse-string suture Fluoroscopy revealed the presence of mucosal folds at the intestinal-cloacal junction (fig 6) These folds, called Houston's valves, demonstrated 95 per cent competency even when the cloaca was overdistended at 40 cm of pressure, far above normal cloacal pressures

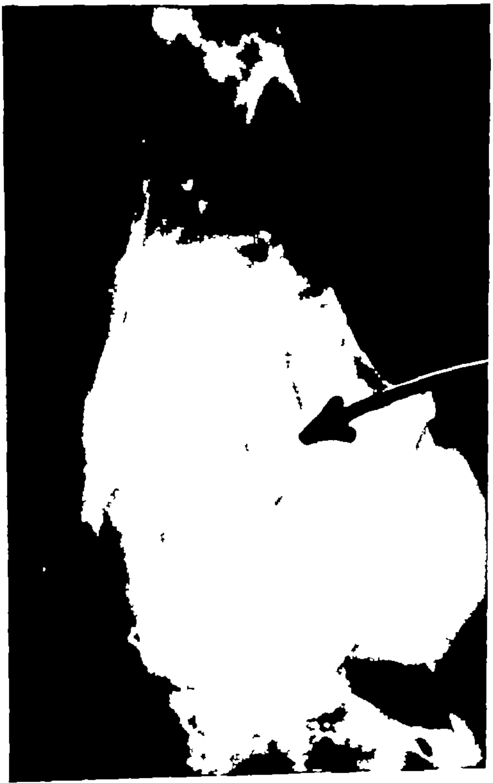

FIG 6 Valves at intestinal cloacal junction in hen which prevent reflux Demonstrated by barium enema at 40 cm pressure

	VOLUME IN BOWEL	SURFACE AREA EXPOSED	% ISOTOPE ABSORBED (4 hrs)
MAN	100cc	600cm^2 (±10%)	89 8 (Mean)
FOWL	10 cc	60 cm^2 (±10%)	7 6 (Mean)

Fig 7 Absorption of isotopes related to surface area exposed (mean of all experiments)

In all the electrolyte experiments in chickens, examination of the mucosa for staining with indigo carmine showed that the test solution never reached higher than 10 cm above the anus and that there was no reflux either into the oviduct or ureters

Surface area exposed In attempting to correlate the quantity of electrolyte absorbed in man and the fowl in relation to bowel surface exposed, the comparisons shown in figure 7 were made The isotopes represent the mean of all experiments

The bowel area exposed to the electrolyte solution in man was estimated by placing the same quantity of thin colloidal barium rectally and observing on x-rays the distance this mixture diffused over a period of four hours Although the spread is not identical to that of isotope-labelled solution, this distance and estimates of bowel diameter were used to obtain a rough estimate of the area of bowel surface exposed

The calculations indicate that the volume of isotope solution (100 ml) instilled in man exposed approximately comparable mucosal areas as the smaller amount (10 ml) instilled in the fowl

Apparently factors other than surface area account for the resistance of the mucosa of the cloaca which keeps absorption at such low levels In discussing the problem of reabsorptive acidosis in man after ureterointestinal anastomosis Creevy,[9] Boyce,[10] and others[11] [12] have emphasized the need for transplanting the ureters to the distal part of the colon Although there is reflux regardless of site this facilitates frequent bowel evacuation, decreasing the time urine is in contact with the bowel mucosa

Early investigators of poultry physiology believed that the cloaca reabsorbed considerable amounts of water from the urine [13] The results of more recent and comprehensive experiments indicate, however, that while some water is reabsorbed it is in insignificant amounts [14]

[9] Creevy C D Some observations upon absorption after ureterosigmoidostomy J Urol 70 196-202 1953

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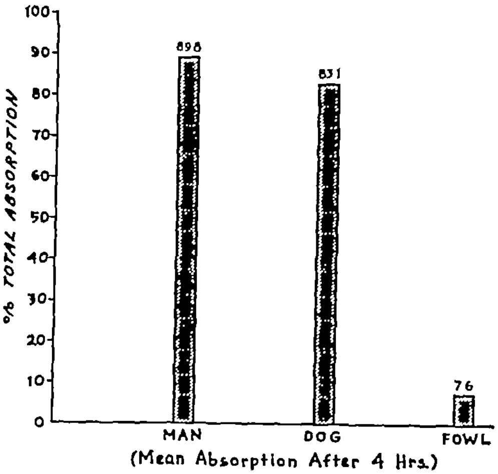

FIG 8 Comparison of isotope absorption in man, dog, and fowl

SUMMARY AND CONCLUSIONS

It has been interesting to verify the assumption that urine is contained in the cloaca without disturbance of electrolyte balance Apparently the problem is a simple one The cloaca, with histologic resemblance to the large intestine, has more nearly the physiologic characteristics of a urinary bladder (fig 8) In contrast to the rectosigmoid which absorbs almost all sodium and iodine the cloaca absorbs hardly any

To eliminate the possibility that frequent emptying would minimize absorption from the cloaca, the anus was sealed during our experiments—carried out for a sufficient period of time for equilibrium to be reached between the fluids of the cloaca, the circulating blood, and tissue spaces

Apparently the urine of the bird contains no constituent, such as an enzyme, which prevents its absorption Addition of bird's urine to solutions placed in the rectosigmoid of dogs exerted no deterrent effect upon its absorption Nor did varying the concentration of the instilled solutions exert any discernible effect

Finally, the area of exposed mucous membrane is no significant factor Comparison shows that the relationships of the surface area to the fluid content parallel each other in the rectosigmoid and the cloaca

We are left only with the remarkable physiochemical adaptation of the cloacal wall to explain the bird's protection against reabsorptive acidosis

There is no obvious clinical application we can make of this knowledge However, in humans there may be some degree of individual adaptation following diversion of the urine to the rectosigmoid It has seemed to us that children who have undergone ureterosigmoidostomy appear to be more adaptable to the formation of a cloaca than do adults There have been fewer electrolyte disturbances and when they do occur they seem more transient in the child than in the adult Whether this represents only a renal compensatory mechanism, or whether there are also compensatory changes in the colon which affect its absorptive capacity is still unknown It is possible that the lesser incidence of pyelonephritis and hydronephrosis in the child may be reflected in a better electrolyte balance

We are making comparative studies following ureterosigmoidal anastomosis in the child and adult to determine whether there is any difference in the rate of absorption of tagged electrolytes

While it has been illuminating to investigate the cloaca as far up as Houston's valves, we are intrigued with speculations as to what would happen if the ureters of the fowl were re-implanted in the upper intestinal tract In studies performed in 1940 we found that re-implantation of the ureters into the cloaca was frequently attended by the development of upper urinary obstruction and ascending infection, indicating that the fowl is not immune to these complications of the human [1]

It would seem reasonable that under suitable conditions the fowl will also develop hyperchloremic acidosis

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CONGENITAL PATENT URACHUS

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The complex group of changes which occur during the intrauterine maturation of the urinary tract gives rise to several anomalies including those of the urachus The occurrence of patent urachus is of sufficient rarity, however, that no one surgeon can obtain familiarity with the condition through personal experience It is the purpose of this paper to present from an analysis of the reported cases the most favorable methods of diagnosis and treatment A brief discussion of the embryology and anatomy is also included for completeness One hundred cases including four previously unreported cases were used for this analysis Three of the four unreported cases were seen at Charity Hospital of New Orleans, the remaining one at Hotel Dieu in New Orleans Escape of urine from the umbilicus at birth or shortly following separation of the cord was the criterion for acceptance of each case

The original observation and description of congenital patent urachus were by Bartholomaeus Cabrolius in 1550 Vaughan in 1905, Herbst in 1937, and Leitch in 1950 reviewed the literature but included both acquired and congenital cases Many of the authors who reported acquired cases considered them as manifestations, in adulthood, of a congenital disorder Acquired urinary fistula at the umbilicus is never due to a patent or persisting urachus, therefore only the congenital variety is considered in this paper Further reviews have been made which included cases that were not patent throughout These cases should be classified as partially patent urachus or urachal cysts and considered separately

INCIDENCE AND CLASSIFICATION

There are few figures which accurately reflect the incidence of congenital patent urachus From 200,000 admissions to the Children's and Infant's Hospital in Boston the diagnosis was made three times From 15,000 admissions to the Brady Urological Institute the diagnosis of patent urachus was also made three times but this figure includes acquired type cases Wilmoth reports four cases from 5,840 admissions to the U S Marine Hospital In none of the cases reported by Wilmoth did the lumen of the urachus communicate with the bladder lumen The above figures, which include acquired patent urachus and partially patent urachus, give the impression that the condition is more common than is the true case From 1,168,760 admissions to Charity Hospital of New Orleans from 1936 to 1956 the diagnosis of congenital patent urachus was made only three times Figures to express the ratio of the occurrence in males versus females have also included the error induced by including acquired cases These figures have ranged from 2 1 to 9 1 Cullen's review included only congenital cases and the ratio from his review was 2 1 From the 100 cases reviewed here the incidence in males was roughly three times that found in females

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The age range of these cases was from birth to 62 years All cases involving older age groups had experienced an earlier closure or had gone untreated

Congenital patent urachus is classified under anomalies of the urachus Other anomalies include urachal cyst, and partially patent urachus From the pathological examinations reviewed in this series three distinct stages of patent urachus exist

Stage 1, persistence of fetal bladder without descent This stage results in the bladder opening at the level of the umbilicus through a widely patent urachus

Stage 2 persistence of fetal bladder with descent This stage represents cases in which bladder is in normal position but abnormally formed the urachus being a double funnel which is narrowed only in the middle segment

Stage 3 arrested closure of the urachus In this stage the bladder is normal in position and shape the urachus is a narrow tube of fairly uniform diameter This classification is a clinical one which is useful in the treatment of this condition X-ray studies demonstrate well the stage in which any particular case lies The corrective operative procedure will vary slightly with each stage

EMBRYOLOGY AND ANATOMY

The allantois a transitory fetal structure given off from posterior end of the primitive intestine first presents as an endodermal diverticulum. This diverticulum pushes into the mesoderm forming the belly stalk That part of the primitive intestine from which the allantois forms has already been differentiated into the cloaca The urorectal septum grows back from between the allantois and the yolk sac to divide the primitive gut into an upper part (intestine) and lower part (bladder) The bladder is a distinct structure at two months' gestation and is continuous with the allantois The intra-abdominal part of the allantois is the urachus That part of the allantois contained in the umbilical cord persists until birth in more or less rudimentary form There is disagreement as whether the bladder is formed from the cloaca or from the allantois It is further stated by some authors that the urachus is also formed from the cloaca and not from the allantois

In man the allantois never becomes saccular since it does not function as a receptacle for the excretion of the primitive kidneys The only significant functional feature of the allantois lies in the blood vessels which accompany it and place the embryo in close relation to the maternal circulation Failure of the urachus to close into a solid cord at the fourth or fifth month of gestation results in a patent urachus Begg believes that descent of the bladder brings about stretch atrophy of the urachus Failure of the urachus to close is therefore due to failure of the bladder to descend This theory is not supported however by the many cases in which the bladder has assumed its normal position Failure of the bladder to descend is considered an effect rather than a cause Patency of the urachus is due to a primary defect in development of the urachus In some cases lower urinary tract obstruction undoubtedly contributes to this retained patency

The urachus is a tubular connection between the bladder and umbilicus which lies between the peritoneum and the transversalis fascia This plane is called the space of Retzius The urachus is surrounded by a fascial sheath called the umbilical vesical fascia, this is separated from the transversalis fascia by the umbilical prevesical fascia A definite reflection of the peritoneum into a mesourachus is present in many cases

The urachus is tortuous in its course, and acts to take up slack during bladder contraction A central point for bladder contraction is provided by the continuation of bladder muscle over the urachus

The urachal arteries arise from the superior vesical arteries They give off anastomotic branches to the branches of the superior vesical arteries of the opposite side and to branches of the epigastric arteries which re-pierce the transversalis fascia

Histologically the urachus is composed of three distinct layers of tissue The inner layer is modified transitional epithelium which has three well defined layers of cells No basement membrane is present The middle layer is connective tissue containing blood and lymph vessels The outer layer is composed of involuntary muscle which consists of both longitudinal and circular components The adventitial coat of the bladder is not continued over the urachus The presence of a transverse fold of bladder mucosa at the junction of the urachus and bladder was described by Wutz, but this finding has not been confirmed by other authors A section of the urachus from case 1 is shown in figure 1

DIAGNOSIS

The diagnosis of congenital patent urachus is usually made from the leakage of urine at the umbilicus following separation of the cord The umbilical urine flow varies from a few drops to a full stream The leakage is likely to be greater when the patient is prone, straining, or voiding An umbilical tumor of varying size, shape, and color was present in 44 per cent of the cases This tumor is that remaining portion of the cord which is being nourished by the urachal arteries, but in some cases is due to an associated umbilical hernia The umbilical mass is

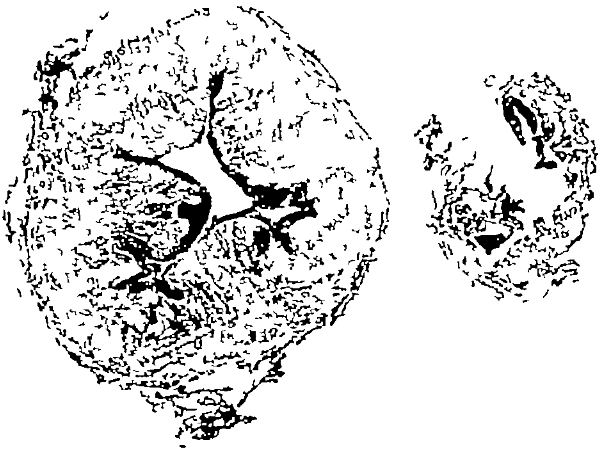

Fig 1 Case 1 Low power magnification of section through patent urachus and one of umbilical arteries

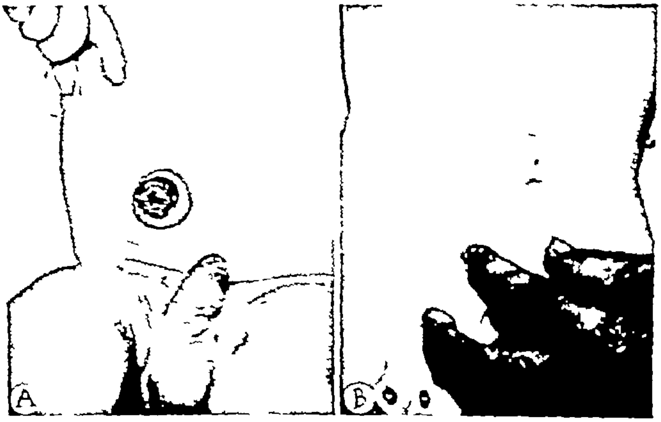

FIG 2 Case 1 Pre and postoperative views of umbilical region

covered in part by the mucosa of the urachus and partially by normal skin An illustration of the umbilical tumor from case 1 is shown in figure 2 A The umbilicus may appear normal or be marked only by small radial folds in the periumbilical skin Leakage of urine causes excoriation and irritation of the periumbilical skin but not the marked skin digestion found in association with a patent omphalomesenteric duct If infection is present the appearance of the umbilicus and the characteristics of the draining fluid will be altered in proportion to the degree of infection

The presence of an abnormally large cord or other cord anomalies at birth is commonly associated with a patent urachus Reflux of urine through the urachus into the cord can cause cystic dilation prior to separation The presence of a patent urachus also causes a delay in separation of the cord The connection between the umbilicus and bladder can be proven in several ways Proof by analysis that the draining fluid is urine is the most simple method The introduction of dye such as methylene blue and its subsequent appearance from the urethra proves an existing connection A blue discoloration of the umbilical fluid following injection of 4 per cent indigo carmine is also diagnostic Proof of a bladder connection by the use of catheters or sounds introduced into the umbilicus may be misleading unless they are seen in the bladder at cystoscopic examination or exit through the urethra A urachal cyst which communicates with the umbilicus cannot be ruled out unless passage of these instruments into the bladder can be proven Cystoscopic examination is helpful in determining the stage and size of the patent urachus and in evaluating the degree of any lower urinary tract obstruction X-ray studies should be done to rule out lower urinary obstruction and upper urinary tract anomalies Subcutaneous injection of diodrast in saline is the method of choice in the newborn Fluids should be withheld 12 hours prior to the injection of 80 cc saline with 20 cc of 35 per cent diodrast The scapula area is the injection site Films are taken every 10 minutes for 50 minutes For visualization of the urachus and lower urinary tract diodrast or diodrast in acacia is injected through a blunt-nosed nozzle into the umbilical opening Lateral films should be completed while the contrast medium is being

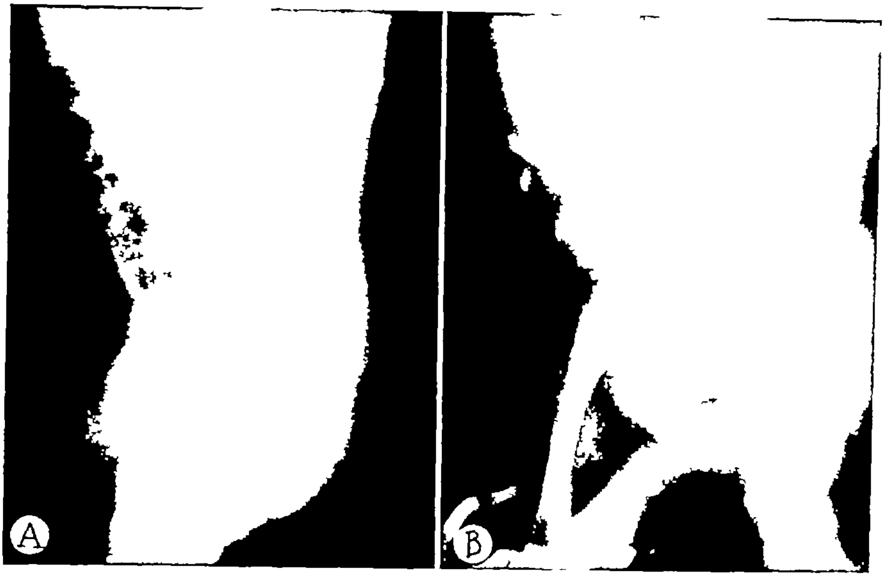

FIG 3 Case 1 *A*, cystogram, lateral view, shows patent urachus *B*, cystogram antero posterior view, shows normal anterior and posterior urethra Urachus also demonstrated

injected and followed by other views Care should be taken that the infant is not subjected to an overdose of radiation by too many x-ray studies The cystogram showing the urachus and lower urinary tract from case 1 is shown in figure 3 Differential diagnosis includes omphalitis, umbilical granuloma, omphalocele, and patent omphalomesenteric duct When doubt exists as to the presence of a patent omphalomesenteric duct, x-ray studies of the upper gastrointestinal tract should be done These two congenital anomalies existed together in five of the cases of this series

TREATMENT

Many methods for the treatment of patent urachus have been devised in the past These include circumcision, cautery, ligation, compression, simple suture, and surgical excision The result of each type treatment is shown in table 1

The best results have been from an extraperitoneal approach with complete surgical removal of the urachus Some authors suggest opening the peritoneum lateral to the urachus in order that a finger may be inserted to ascertain that no bowel segment is adherent to the urachus This procedure is not necessary in cases where infection has not yet occurred More conservative methods of treatment do effect a closure in some cases but are prone to complications Recurrence of the umbilical fistulas, formation of a urachal cyst, development of carcinoma of the urachus, and later accidental surgical division during adulthood are some of the complications which result from conservative treatment

Some authors have advocated postponing surgery until after the first year of life This practice only allows for infection to occur producing adhesions which make later surgery more difficult and dangerous Surgical intervention should not be delayed once the diagnosis is made if no delaying factors are present These factors include lower urinary tract obstruction, infection, multiple anom-

TABLE 1 *Treatment of congenital patent urachus Type of treatment and results from 100 cases including four previously unreported cases*

Type of Treatment	No	Results					
		Closure	Non closure	Re opened	Devel oped ca	Devel oped cyst	Expired
1 Ligation of umb tumor	6	4	1	1	0	0	0
2 Ligation, excision of umb tumor	4	3	1	0	0	0	0
3 Ligation, caut of umb tumor	3	2	1	0	0	0	0
4 Caut of umb tumor	13	3	6	0	3	1	0
5 *Incision, caut of umb tumor*	1	1	0	0	0	0	0
6 Simple suture of umb tumor	5	2	1	2	0	0	0
7 Umb tumor sutured, strapped	2	2	0	0	0	0	0
8 Umb tumor taped or strapped	5	2	3	0	0	0	0
9 Circumcision only	5	2	3	0	0	0	0
10 Urachus excised (intraperitoneally)	12	11	0	0	0	0	1
11 Urachus excised (extraperitoneally)	31	31	0	0	0	0	0
12 Abd surgery, urachus untreated	3	0	0	0	0	0	3
13 Spontaneous closure	3	2	0	1	0	0	0
14 No treatment given	21	0	0	0	0	0	5

Index to abbreviations Umb —Umbilical, Caut —Cauterization

alies, and inadequate renal function After urinary obstruction has been removed the urachus should be excised even if spontaneous closure has occurred in the interval Excision of the urachus is best accomplished through a midline incision, the upper pole of which encircles the umbilicus The postoperative results of this type incision are shown in figure 2, *B* The urachus is exposed after separation of the abdominal muscles by division in the midline A probe or indwelling catheter placed in the urachus facilitates its isolation Methylene blue assists in isolation in cases where the urachus is too small to admit a probe or catheter The urachus, once freed, is then ligated and divided at the bladder junction In stage 1 and 2 segmental resection of part of the bladder is necessary to remove completely the urachus and restore the normal dome shape to the bladder The bladder is then closed in a purse-string manner, or with interrupted sutures Drainage is advocated due to high rate of wound infection An indwelling catheter should be placed in the bladder for at least five days postoperatively With radical excision of the urachus complications can be minimized

CASE REPORTS

Case 1 D B , a five-week-old white male infant, was admitted to Hotel Dieu in New Orleans on November 27, 1954, with a chief complaint of passing urine through the umbilicus On physical examination a red umbilical tumor 2 by 5 cm in diameter was present Urinalysis and blood studies were essentially negative A cystogram made November 29 confirmed the diagnosis of congenital patent urachus On November 30, intravenous pyelograms revealed no further anomalies of the urinary tract Renal function tests showed good bilateral secretory activity On December 1, under general anesthesia, an elliptical incision was made around the umbilicus and expended downward Using a probe in the urachus, the tract was freed down to the bladder The urachus was then ligated and excised The bladder opening was closed with 00 cotton The incision was closed over a rubber drain and a plastic procedure done to reconstruct the umbilicus The specimen consisted of the umbilicus and an attached tubular structure The lumen of the urachus varied from 4 to 7 mm in diameter and was lined by transitional epithelium A urethral catheter was inserted and retained for five days postoperatively Convalescence was uneventful and the patient was discharged on the fourth postoperative day A two-year followup revealed no urinary complaints and no signs of recurrence

Case 2 I S, a two-month-old colored male infant, was admitted to Charity Hospital of New Orleans on April 28, 1954 with a chief complaint of passing water through his navel The patient's parents gave a history of leakage of urine from the navel since separation of the cord This leakage was more pronounced when the patient strained or coughed On physical examination fluid could be expressed from the umbilicus which proved to be urine by analysis A cystogram failed to reveal a connection between the bladder and umbilicus A plain urogram and an intravenous pyelogram showed no abnormalities of the urinary tract On May 7, under general anesthesia, a midline incision was made from the umbilicus downward A fusiform catheter was passed from the umbilicus into the bladder The urachus with its associated mesourachus was dissected free The peritoneum was opened for this procedure The urachus was ligated and excised from the bladder The bladder was then closed with two figure of eight 00 chromic sutures The patient went into cardiac arrest before closure was completed Cardiac massage was then done through a left thoracotomy incision Both incisions were then closed Following closure the tank supplying oxygen was found to be empty The patient died on May 10 from diffuse brain damage produced by anoxia Examination of the operative specimen revealed cystic dilation of the urachus with connections to both the bladder and the umbilicus

Case 3 C H, a six-week-old colored male infant, was admitted to Charity Hospital of New Orleans on February 3, 1953 with a chief complaint of persistent projectile vomiting The parents also gave a history of the leakage of urine from the umbilicus since separation of the cord On physical examination a left hydrocele was noted in addition to the patent urachus On February 4, under general anesthesia, a supra-umbilical incision was made across both rectus muscles The intestines were found to be normal The urachus was dissected free retroperitoneally and excised from the bladder and umbilicus The bladder incision was inverted and closed The hydrocele was repaired and the incision closed Convalescence was uneventful and the patient was discharged on the fifth postoperative day Pathological examination confirmed the diagnosis of congenital patent urachus

Case 4 This male infant was born July 30, 1943 and died shortly thereafter from multiple congenital anomalies Autopsy revealed a congenital patent urachus in addition to other anomalies

SUMMARY

Patent urachus is a rare congenital anomaly, only 3 cases having been seen in more than 1,000,000 admissions to Charity Hospital of New Orleans

The fetal structure from which the urachus develops is still controversial

Congenital patent urachus is classified under diseases of the urachus and three stages are given

The diagnosis is made from the flow of urine from the umbilicus, further studies should be done to rule out lower urinary obstruction or other urinary anomalies

The treatment of choice is given from an analysis of 100 cases

Four previously unreported cases are presented among which there were two fatalities

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A CASE REPORT OF A DOUBLE BLADDER AND DOUBLE URETHRA IN THE FEMALE CHILD

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Duplications of the urinary tract are very common This however, is not true of the female bladder and urethra

Burns[1] has cited a total of three cases of complete duplication of the urinary bladder with complete duplication of the urethra, in the female [2-4] (All were stillborn with other anomalies) Hinkel[5] has added a fourth case of a double bladder, double urethra found in a 62-year old white woman, who also had a double anus and colon which were functional In all four cases the double bladder was divided in the midsaggital plane and the two urethras were side by side

In suggesting a classification of double urethra Irmisch and Cook[6] list four categories, three of which are based on the position of the additional urethra to the penis or to its function in the male The fourth category is urethral fistula They apparently allow no place for the occurrence of complete double urethra in the female patient

Danreuther[7] reported a case of a 50-year old white woman with an accessory opening beneath the normal urethra He passed a urethral catheter and found its tip in the bladder lumen to the right of the right urethral orifice He reported his case as a double urethra DeNicola[8] recorded a case of a female child with an accessory urethral channel also located beneath the normal urethra which was treated successfully with sodium morrhuate

Partial duplications of the female urethra have been reported by Schinagel[9] in the country and by a few foreign writers, notably Kubig,[10] who felt that at the time of his case (1926) complete duplication of the female urethra as a congenital anomaly had not yet been reported to the acceptability of the medical profession He cited the hypothesis of VonBolk, who believed that the formation of this anomaly, namely, double urethra in the female, was highly unlikely to ever be formed

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[10] Kubig, G Doppelte Urethra Zentralblatt Gynak **50** 3125–3128 1926

CASE REPORT

Case No 312883 was a two-year old white female child who was admitted to University Hospitals on January 21 1957 and discharged on January 28 1957 Chief complaint as given by the parents was "two vaginas" The history revealed that this was the first and only child of this couple The pregnancy and delivery were uneventful The delivery weight was 6 pounds 9 ounces Six weeks check-up revealed an essentially normal white female child However at that time it was noticed she had a septum which separated her vagina into two components a right and a left side It was decided at that time to allow for further growth and development before evaluation was made The development, both physical and mental during the ensuing two years was entirely normal She had never been incontinent She was trained and developed toilet habits at approximately 18 months of age At present she is entirely continent of bladder and bowel

Physical examination revealed a well developed well nourished bright-eyed youngster normal in all respects except for the inspection of the perineum (fig 1)

Gross inspection of the perineum revealed a normal single clitoris The labium majora on each side was essentially normal and single In place of the midline structure where the urethra and vaginal orifice are normally seen was present a midline septum extending from the upper portion of the vestibule to the lower portion near the posterior fourchette There was a small skin tag present at the lower portion of this septum thought by inspection to be the remnant of the median raphe and the labium minora To each side of this septum were found two orifices an upper and a lower The upper orifice was somewhat smaller than the lower The lower orifices on each side were thought to represent a right and a left vaginal outlet Catheterization of the upper left orifice with a size 8 Robinson catheter produced 8 cc of clear yellow urine

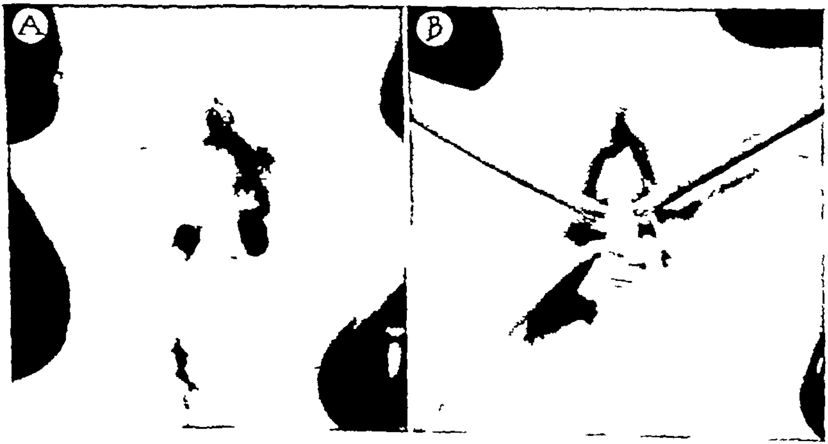

Fig 1 A single clitoris and anus normal labia majora with diseptate vagina and double urethral orifices Low midline tissue is thought to be labia minora and median raphe B size 8 Robinson catheter in each urethral orifice and in each vaginal outlet

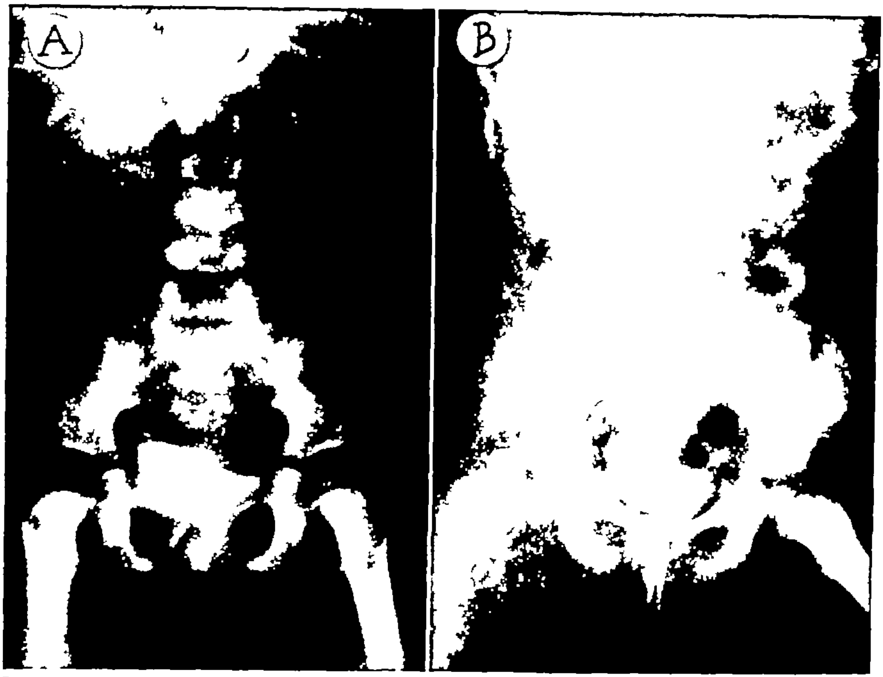

FIG 2 *A*, 5 minute intravenous pyelogram shows complete duplication of bladder Note normal upper urinary tract Lower right ureter is visible *B*, bilateral cystogram demonstrates double urethra, double bladder

Catheterization was then carried out on the right side through the right upper orifice This catheterization produced another 6 cc of clear yellow urine Both of these orifices were easily catheterized The child later was observed during the act of micturition and found to void easily and simultaneously through both urethras

Complete blood count, urinalysis, blood urea nitrogen and fasting blood sugar were all within normal limits A chest x-ray taken on January 23 was normal The pelvis and lumbar spine films were negative for bone or joint disease An intravenous pyelogram, taken on January 25, 1957, revealed two normal kidneys and a normal single ureter on each side This girl, however, had a complete duplication of the bladder (fig 2, *A*) A cystogram (fig 2, *B*) showed complete duplication of bladder and urethra

A cystoscopic examination disclosed a normal ureteral orifice on each side of a normal trigone There was a complete septum in the midline which appeared thin, nonmuscular, and lined by mucous membrane

With a size 8 Robinson catheter in each urethra, methylene blue was injected through the left catheter No dye was obtained from the right catheter Three days later methylene blue was injected through the right urethral catheter and no dye was obtained from the left side

A panendoscope was then introduced into the vaginal outlet and a single cervix was easily seen It appeared just to the right of the midline and was best seen through the right orifice The septum was found to extend into the vaginal outlet for one-third of the distance of the vagina The proximal portion was a single normal appearing structure A barium enema demonstrated a single colon with normal position and function It was felt that although the lower urinary tract was extremely unusual, the anatomical arrangements were entirely physiological and compatible with life We advised against removal of the vaginal septum until a later date, perhaps prior to the onset of menses

EMBRYOLOGY

This anomalous condition in a human female is characterized by a completely symmetrical mid-sagittal division of the urinary bladder, urethra, and vulvar end of the vagina The fact that the major portion of the vagina, the cervix, and rectum are single, and that there are no other detectable anomalies of skeleton or viscera, makes this condition difficult to explain

There seems to be little point in attempting to correlate it with dorsoventral duplication of the urethra in the human male, or with irregularly septate bladders, some of which may be congenital, but many of which more probably result from diverticula Certainly, this is not a clear-cut case of ventro-caudal twinning, as there is no duplication of the phallus, nor widening of the pubic symphysis (split pelvis) Therefore, because this anomaly is so unique, and since no adequate explanation of it has been offered previously, we shall suggest an explanation purely on the basis of the known anatomy of this case, together with the generally accepted developmental history of the region[11] and certain theoretical concepts derived from experimental embryology

The suggestion was made by one of us (E J S) that the anomaly may have been initiated by doubling of the original endodermal allantoic anlage Although we do not know of an account of a double allantoic duct, this assumption seems to be the most reasonable starting point

It is conceivable that in the early embryonic shield stage an abnormal growth and widening of the presumptive ventral wall of the hind-gut, i e , upper caudal wall of the definitive yolk-sac, could have resulted in twin endodermal allantoic anlagen Later, as the bladder and urogenital sinus began to separate from the rectal portion of the cloaca, one would expect the mid-sagittal septum between the two allantoic ducts to be perpetuated caudally as a ventral element of the frontally oriented uro-rectal membrane These so-called "membranes" are nothing but mesenchyme which hypertrophies to occupy the space left by the endodermal elements which are separating from one another by differential growth and movement of their epithelial portions This would then result in the progressive formation of a pair of urachuses, bladders, and urogenital sinuses Each bladder would then receive only the ipsilateral ureter, as occurs in this case The paired external ends of the urogenital sinuses would be expected to induce a local widening or doubling of the ectodermal urethral plate which, when canalized, would result in paired external urethral orifices

The junction of the müllerian ducts with the urogenital sinuses is known to occur relatively late (30 mm)[12] Thus, there is no reason why the two müllerian ducts might not have fused in the normal manner to form a single uterovaginal anlage Since the caudal end of this is a relatively broad epithelial mass, it could easily attach to the dorsal walls of both of the narrow and closely approximated urogenital sinuses This would presumably induce the normal hypertrophy of sinus epithelium (vaginal bulbs) from each[12] Since it is probable that the lower one-fifth of the definitive vagina is formed from this anlage of sinus epithelium, then with double sinuses one would expect paired external vaginal orifices with a single proximal vaginal tract, as does occur in this individual

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[11] Hamilton, W J Boyd J D and Mossman, H W Human Embryology, 2nd ed Cambridge Heffer and Sons, 1952

The umbilicus seems entirely normal, thus, if a doubling of the allantois did occur, the two anlagen must have been very close to one another There is no reason to expect them to be otherwise The single phallus, vagina proper, and rectum indicate a very localized "twinning" effect The external genitalia are normal, except for the paired urethral and vaginal orifices, and an inconspicuous elevation near the widened posterior commissure This may be a rudimentary medium labium minorum The anoperineal raphe is very faintly visible, and seems to be single This, with the single phallus and anus, suggests that any doubling of the anourethral epithelial plate must have been confined to its middle portion

CONCLUSIONS

A case of a complete duplication of the bladder and urethra with the presence of a biseptate vagina has been presented with review of the pertinent literature

An embryological explanation has been offered

This anomaly, although extremely unusual, is entirely physiological and compatible with life

To our knowledge that is the first time this specific type of duplication has been reported in a living female infant (The other four cases of double bladder, double urethra in the female included three stillborns with other anomalies outside the genitourinary tract, and a fourth case which represented caudal twinning of the entire hindgut and genitourinary tract)

This is the twelfth case of a complete double urethra, double bladder in the literature

The isolated finding of a double urethra in the female has not as yet been reported as a side-to-side structure

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SURGICAL CORRECTION OF HYPOSPADIAS

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The ideal operation for correction of hypospadias remains as elusive today as it was in 1837 when Diffenbach allegedly first tried to correct this anomaly and failed Innumerable surgical procedures have been advocated since then but each has been found to have its respective shortcomings Since different surgeons do not achieve comparable results with the same techniques, it is unlikely that any therapeutic plan will ever attain universal favor This report is a review of personal experiences in the management of hypospadias and associated deformities during a period of 6½ years

CHORDEE AND ALLIED INITIAL PROBLEMS IN 172 CASES

From August 1950, to February 1957, 172 patients were operated on because of chordee, hypospadias or the sequelae of previous surgical procedures When first seen, these 172 individuals did not present the same problem and did not require identical treatment Chordee was present in 107 cases and absent in 65 Seven basic categories were represented

1 Meatal stenosis without chordee (14 cases) It is generally agreed that mild hypospadias without chordee should not be disturbed during childhood and rarely requires surgical treatment in adult life One notable exception is the patient with a minute urethral meatus and a poor urinary stream Meatotomy is indicated, but if this is performed in the usual manner valuable urethra will be sacrificed and the degree of hypospadias will be aggravated

These patients invariably have a more distal opening or indentation which on probing is found to communicate with another channel (fig 1) This is a separate, short, vestigial, terminal urethra which lies parallel to the one through which the urine passes If the intervening septum is divided, the caliber of the meatus can be increased without sacrificing any of the normal urethra This type of meatotomy sufficed in 14 instances

2 Untreated chordee and hypospadias (83 cases) More extensive surgical intervention becomes mandatory when there is any significant curvature of the penis, irrespective of the location of the urethral meatus Many techniques have been devised for correction of chordee These vary chiefly with the manner in which the hooded prepuce is diverted to the ventral surface of the penis It matters little as to how the skin is revised so long as *all* of the constrictions along the corpora cavernosa are eliminated Duplay's original operation (fig 2) remains the simplest and was employed in most of the 83 cases of untreated chordee with hypospadias

The urethral meatus is left intact Thorough excision of all constricting fibrous bands is preferred even though some authors insist that they need only be di-

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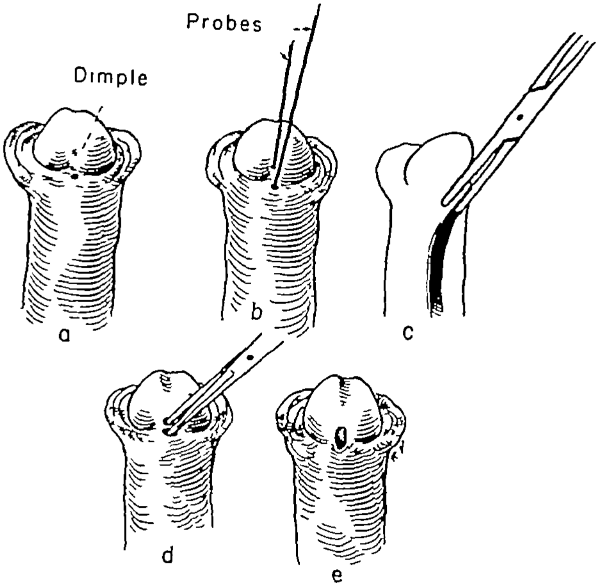

FIG 1 Special meatotomy *a*, Stenotic hypospadiac meatus without chordee *b*, Dimple on glans communicates with separate short channel parallel to normal urethra c, Intervening septum is crushed with small hemostat and (*d*) divided with scissors, thereby enlarging meatus (*e*) without aggravating mild hypospadias

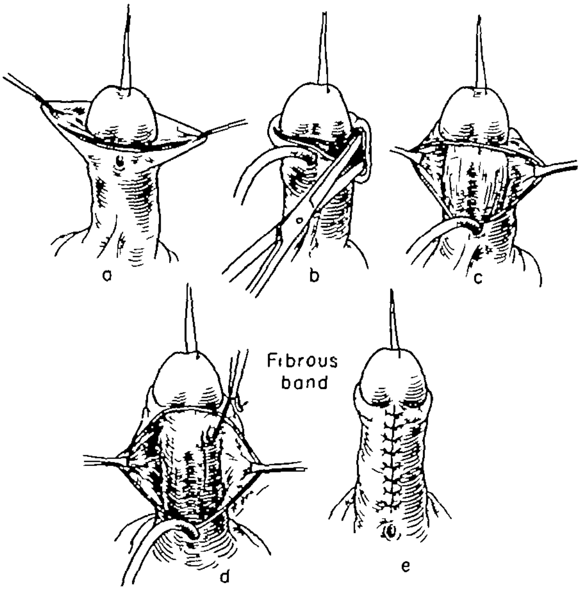

FIG 2 Correction of chordee *a*, Transverse incision distal to meatus is extended into hooded prepuce and (*b*) latter is freed with blunt scissors *c*, Urethra is freed from corpora with an indwelling catheter as a guide *d*, All constricting tissue is excised after freeing penile skin laterally Meatus gravitates to most convenient position—usually near penoscrotal juncture *e*, Penile skin is closed longitudinally with interrupted sutures

vided When the skin is closed longitudinally special precautions should be taken to avoid obliterating the furrow on the base of the glans, for this permits construction of a more desirable type of meatus during the subsequent urethroplasty If such a furrow does not exist, an attempt should be made to create one at the time of the straightening

If urethroplasty is contemplated within the next year, it is advisable to suture the skin with fine wire because it produces a minimum of fibrosis If three or four years may elapse before the next stage, fine catgut suture may be used for closure of the skin An elastoplast dressing is applied to prevent edema, but the displaced meatus is left exposed

An indwelling catheter is employed for 24 to 48 hours in patients of school age The catheter is removed at the end of the operation in younger patients, since postoperative urinary retention is rare in those less than six years of age

There will be less subsequent edema if the dressing is not disturbed until the eighth to tenth day, at which time wire sutures are also removed Thiopental (pentothal) sodium by rectum provides excellent analgesia for the very young patients

3 *Unsuccessful correction of chordee (12 cases)* Twelve patients still had considerable chordee despite from one to five previous operations The author had to operate twice on one patient with chordee before the penis appeared straight Since failure may occur with any method, correction of chordee should not be combined with the definitive type of urethroplasty but should be a separate procedure

Fortunately, most of the patients in this group that required further straightening still had ample penile skin and some degree of hooded prepuce In these patients the condition was corrected by the previously described method But when the prepucial skin already had been diverted to the ventral surface or had been removed by circumcision (as was true in four cases in this series), some form of the well-known Z-plasty had to be employed

4 *Chordee without hypospadias (five cases)* Five patients had marked chordee but the urethral meatus was in normal position at the tip of the glans Although it has been reported that adequate straightening in such cases may result from merely freeing the urethra and providing more ventral skin, this was not true in this group In each of these five cases the urethra was much too short and had to be divided

To assure preservation of the terminal segment it is best to transect the urethra in the vicinity of the penoscrotal juncture rather than near the glans The distal portion is freed, all constricting tissue is excised and additional ventral skin is provided by right-angled incisions into the prepuce or by appropriate Z-plasty

An indwelling catheter is left in both segments of the urethra for approximately one week to prevent stenosis of the distal urethral opening as well as of the new hypospadiac meatus Additional urethra is constructed at a subsequent procedure to bridge the gap between the two urethral segments

5 *Urethroplasty despite residual chordee* (*seven cases*) The most unfortunate individuals were the seven who had urethroplasties before their chordee had been eliminated completely One of these patients had been subjected to 10 operations In three cases the reconstructed urethra was intact and had to be transected as in the preceding group Varying amounts of new urethra had to be sacrificed in the other four cases because of fistulas In most instances the patient literally had to start anew

Pathetic situations of this type emphasize most dramatically the importance of being certain that chordee has been corrected These tragedies can be avoided only by truly honest evaluation of postoperative results

6 *Hypospadias without chordee* (*33 cases*) Five patients had sufficient hypospadias to need surgical treatment despite the fact that they had never had any chordee The old type of urethral meatotomy was responsible for at least three of these

The other 28 patients had been treated successfully for chordee but no attempt had been made to construct the additional urethra Six of these individuals had required more than one straightening operation Eighteen patients had had their chordee corrected by the two-stage Edmunds operation The remaining 10 penises had been straightened in a variety of ways but most of the procedures were variations of the Heineke-Mikulicz principle with the exception of Nesbit's operation The latter has come into favor because it provides a transverse closure at the base of the penis and avoids longitudinal scarring

7 *Postoperative urinary fistulas* (*18 cases*) In 18 cases the chordee had been corrected and one or more attempts had been made to construct additional urethra One patient had had nine previous operations All of these 18 patients had at least one fistula They varied in size from 1 mm to that of most of the pendulous urethra Some also had urethral strictures

It was impossible to be certain of the type of urethroplasty that had been employed in each case But they are known to have included free tube grafts, and Ombrédanne, Thiersch-Duplay, Denis Browne and Cecil operations

Comment There is overwhelming evidence that the straightening operation is not viewed with sufficient respect in some circles Frequently the procedure is much too conservative The original attempt to correct chordee had failed in 19 per cent of the patients in this study Some surgeons who never intend to perform urethroplasties unhesitatingly attempt the straightening Frequently too much skin is diverted to the ventrum for some types of urethroplasty Best results will be achieved when the entire surgical plan is properly integrated and each operation provides appropriate preparations for the next stage

Opinions differ regarding the ideal age for correction of chordee, but most writers agree that the penis should be straightened early in life In the present series chordee was corrected at ages that varied from one to 30 years Twenty-five of 107 patients were operated on successfully for chordee when they were less than 2 years old Operations during infancy require more meticulous dissection but are less formidable than in the older age groups The ideal time seems to be around 18 months of age but most of the patients are not seen until they are much older

After all chordee had been corrected in 140 candidates for primary urethroplasty the urethral meatus was at the penoscrotal juncture in 45.7 per cent on the penile shaft in 25 per cent in the scrotum in 20 per cent and remained on the perineum in the other 9.3 per cent

PROVISION OF NORMAL FUNCTION IN 105 CASES

The calculated risk of fistulas strictures poorly draining pouches hairballs maldirected streams and grotesque deformities must be appraised factually and realistically when one is choosing from the various types of urethroplasty that are still in vogue The desirability of any operation is qualified further by the complexity of the procedure the number of stages that it entails its adaptability to the different problems that may be encountered, the age at which it is most feasible and the type of functional and cosmetic result that it usually produces Personal prejudices unquestionably have colored all attempts to weigh the relative importance of each of these factors

Opinions are especially sharply divided regarding the importance of constructing a glandular segment of urethra Perfectionists have been most insistent that the new meatus be at the tip of the glans Only free or pedicle tube grafts have been capable of providing this with any consistency Deliberate termination of the new urethra on the base of the glans may lack cosmetic appeal but it need not be a functional handicap and it avoids operating in an especially treacherous region

It is generally agreed that there should be an interval of at least six months between correction of chordee and urethroplasty but there is no unanimity of opinion regarding the ideal age for construction of the new urethra Many surgeons readily admit the desirability of correcting hypospadias during the preschool period but question the practicality of plastic operations at that age because of the size of the phallus Treatment in the current series was based on the personal conviction that it is the inalienable right of every boy to be a pointer instead of a sitter by the time he starts to school

It is unlikely that any one procedure will suffice or offer optimal results in all cases Of 117 patients in this series who underwent urethroplasty 105 need no further treatment They conformed to three therapeutic categories each of which was managed somewhat differently These categories consisted of 1) 63 patients who had their meatus at or distal to the penoscrotal juncture 2) 21 patients who had scrotal or perineal hypospadias and 3) 21 patients who had fistulas of varying size and number after unsuccessful urethroplasties prior to admission

1 Penile and penoscrotal hypospadias (63 cases) All untreated penile or penoscrotal hypospadias was treated by a version of the Cecil method

First stage When the meatus is at or just beyond the penoscrotal juncture the technique shown in figure 3 is employed The parallel incisions are joined near the posterior edge of the meatus to avoid difficulty inverting the skin at that point They are not extended onto the glans until the terminal urethra is ready to be constructed The width of the medial strip of skin must be sufficient to provide a tube of approximately the same diameter as the existing buried in the same manner but it is essential also to include a generous portion of the adjacent intact urethra The fact that the penoscrotal segment is unattached eliminates much of the dissection at the second stage

2 *Scrotal and perineal hypospadias (21 cases)* Early in the period covered by this study a few patients with scrotal hypospadias were cured by the Cecil method by interposing a layer of deep scrotal tissue between the scrotal and penile segments of the new urethra The integrity of this intervening barrier is unpredictable and the freeing of new urethra from new urethra can be extremely difficult Eventually urethrourethral fistulas were encountered and the technique was abandoned It is best to confine the Cecil operation to penoscrotal and penile varieties of the deformity

In three cases an effort was made to convert scrotal or perineal hypospadias to the penoscrotal form at the time the chordee was corrected, so that they would be suitable for the Cecil operation The Thiersch-Duplay principle was used as shown in figure 6, *a*, *b* and *c* There was a tendency for the meatus to end up just back of the penoscrotal juncture This was accepted as forewarning of impending difficulties and the plan was discontinued

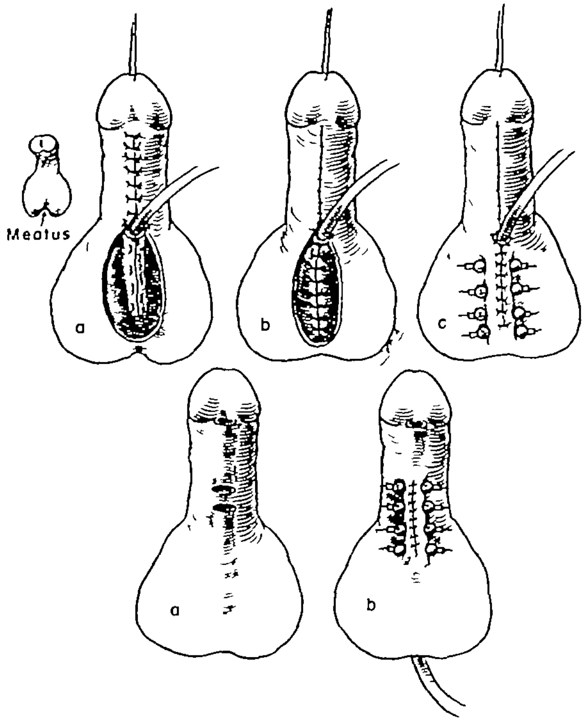

Fig 6 Earlier methods employed in scrotal and perineal hypospadias *a*, At same time chordee is corrected, new urethra is constructed to penoscrotal juncture over indwelling catheter by Thiersch Duplay technique *b*, Deep scrotal tissues are approximated over new urethra *c*, Final closure includes double stop sutures of nylon and interrupted fine catgut sutures in edges of skin *a'*, Independent scrotal and pendulous segments of new urethra constructed by Thiersch Duplay method and (*b*) joined later by Denis Browne principle after diverting urine by perineal urethrostomy

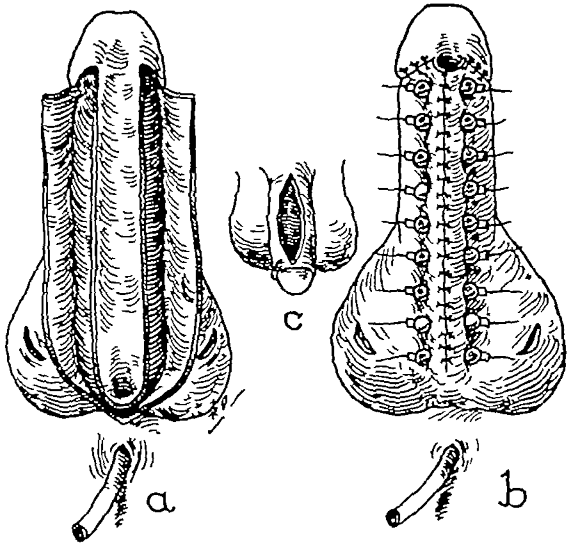

FIG 7 Denis Browne urethroplasty *a*, After diversion of urine by perineal urethrostomy, medial strip of skin is created, and lateral flaps of skin are freed extensively and incised at base of glans Drainage tracts in scrotum are formed through stab wounds and a small area is denuded on each side of glans *b*, Skin is attached to denuded glans with fine catgut sutures and remainder is approximated with double stop sutures of nylon as well as interrupted sutures of fine catgut c, Generous dorsal slit is made

In two cases of perineal hypospadias without residual chordee, the scrotal urethra was constructed in the same manner but an independent pendulous segment was also formed by the Thiersch-Duplay method at the same operation (fig 6, *a′* and *b′*) The intervening defect was treated as a fistula at a subsequent stage

During recent years the Denis Browne operation has been used initially in all cases of scrotal and perineal hypospadias An attempt has been made to follow the technique in every detail as Browne described and demonstrated it The same types of sutures, beads and aluminum stops were employed Urine was diverted by perineal urethrostomy, stab wounds were made in the scrotum and the generous dorsal slit was included routinely (fig 7)

The Denis Browne operation is not mastered promptly or easily Admittedly it was employed in only the most difficult cases in this series Results were unpredictable except for the fact that the scrotal segment always healed Since this is a distinct asset that permits completion of treatment by several methods, it continues to be the choice for scrotal and perineal hypospadias

3 *Fistulas only* (*21 cases*) Just about every conceivable type of urethral defect was encountered in this group Fistulas were cured by variations and combinations of the Cecil and Denis Browne procedures In many instances more than one operation was necessary

A slight modification of the Browne technique (fig 8, *a*, *b* and c) was used for single small fistulas A version of the Cecil method was employed for solitary larger defects Only the midportion of the pendulous urethra was buried in most

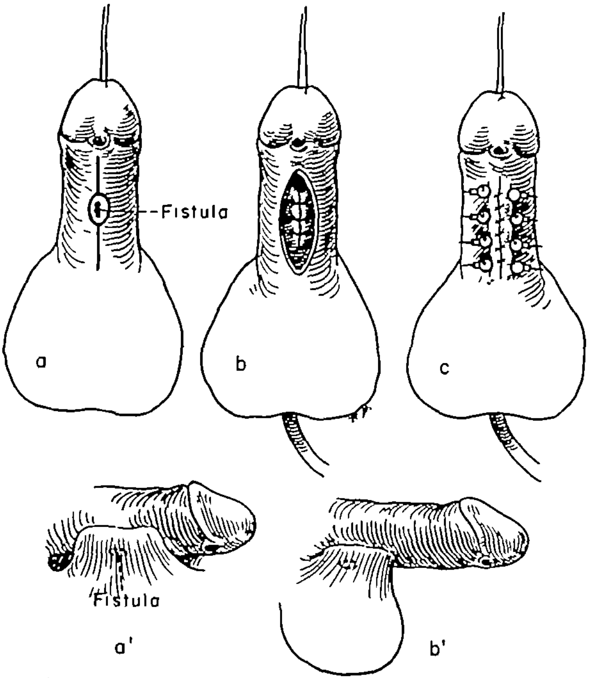

Fig 8 Closure of fistula *a*, Fistula is circumcised and adjacent penile skin is incised *b*, After insertion of catheter perineally and excision of the fistulous tract, adjacent deep tissues are closed with interrupted fine catgut sutures and (*c*) skin is closed by Browne method Larger fistulas are buried in scrotum This may require attachment of only mid-portion of urethra (*a'*) or only proximal segment (*b'*)

Table 1 *How hypospadias was corrected in 105 cases*

	Total	Initial Operation				
		Cecil		Browne		Thiersch Duplay
		Usual	Modified	Usual	Modified	
Total cases	105	57	21	18	4	5
No more treatment	65	37	14	10	4	
Additional surgical procedures						
Cecil	10	2		5		3
Browne	9	2	3	2		2
Duplay	5	4		1		
Secondary closure	6	4	2			
Meatotomy	6	4	1			1
Internal urethrostomy	3	1	1			1
Drainage of scrotum	3	3				

instances (fig 8, *a'*) In a few cases the fistula was just beyond the penoscrotal juncture and only that segment was attached to the scrotum (fig 8, *b'*) When the fistula was near the meatus, the entire terminal portion required revision and was buried, as shown in figure 5

Multiple fistulas were converted to a single large one Frequently they involved

TABLE 2 *Present status of 172 hypospadiacs treated in the period August 1950, to February 1957*

	Patients	
Meatotomy alone performed (mild without chordee)		14
Chordee alone corrected		41
Too young for urethroplasty	15	
Ready for urethroplasty	26	
After urethroplasty		117
Cured	105	
Urethra still buried in scrotum	4	
Persistent complications	8	

TABLE 3 *Complications after treatment of chordee and hypospadias*

	Total	Type of Operation					
		Correction of chordee	Cecil		Browne		Thiersch Duplay
			Usual	Modified	Usual	Modified	
Total operations	253*	107	72	23	28	13	10
Fistula							
Temporary	14		10	1	3		
Persistent	27		4	3	12	3	5
Wound separation	8	2	4	2			
Retracted meatus	9		4	2	3		
Residual chordee	1	1					
Stricture							
Meatal	16	4	9	2			1
Deep	3		1	1			1
Excessive bleeding	4		4				
Keloid	1				1		
Total complications	83	7	36	11	19	3	7

* 91 second stages of Cecil operation not included

practically all of the pendulous urethra Some solitary ones were equally extensive The conventional Cecil operation (fig 3) was used in these situations

Comment All of these operations can be performed just as easily at the age of four or five years as at later ages Twenty-six patients were cured before they started school The others were in older age groups when first seen Nevertheless, 60 per cent of the 105 who have completed all treatment did so before the age of 12 years

Although 105 individuals need no further treatment, only 65 were cured by the author's initial efforts Additional surgical procedures were necessary in the other 40 cases (table 1) By the time all of these 105 patients were cured, 88 conventional or modified Cecil operations had been performed, the Denis Browne principle had been used 31 times, the Thiersch-Duplay procedure had been employed 10 times, and 18 relatively minor operations had been necessary Patients who had not been subjected to previous urethroplasties required an average of 2 2 operations for construction of a suitable, intact urethra

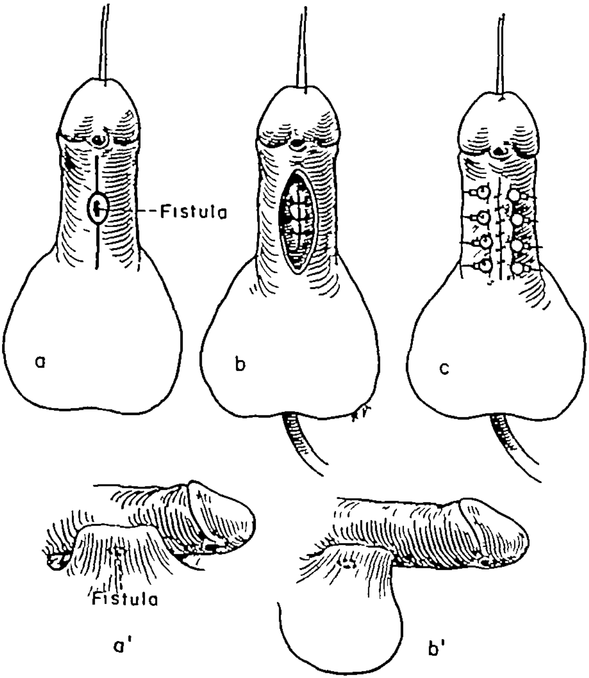

FIG 8 Closure of fistula *a*, Fistula is circumcised and adjacent penile skin is incised *b*, After insertion of catheter perineally and excision of the fistulous tract, adjacent deep tissues are closed with interrupted fine catgut sutures and (*c*) skin is closed by Browne method Larger fistulas are buried in scrotum This may require attachment of only midportion of urethra (*a′*) or only proximal segment (*b′*)

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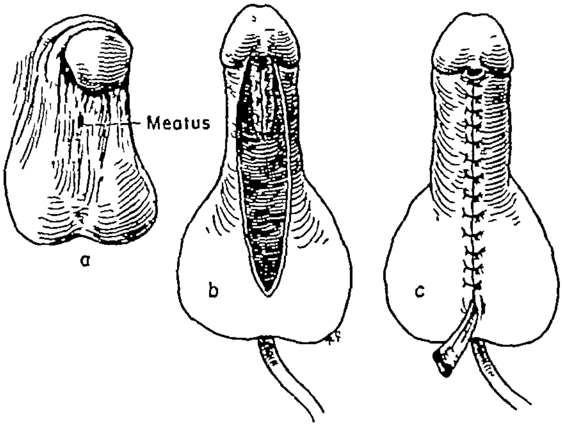

FIG 9 Revision of new meatus When meatus retracts into scrotum (*a*) following first stage of the Cecil operation, a new terminal segment is constructed by the Thiersch-Duplay method (*b*) at same time penis is freed from scrotum Urine is diverted by perineal urethrostomy Skin is closed and scrotum is drained in usual manner (*c*)

Wound separation Obviously all fistulas were associated with some degree of wound separation but the term is reserved at this time for unique situations

Six patients had so much separation of the tissues along one juncture between penis and scrotum a week after the Cecil operation that the indwelling catheter was exposed for considerable distance Persistent fistulas undoubtedly would have developed There was prompt healing in each case after simple secondary closure of the skin No attempt was made to do anything about the urethra per se The entire new urethra is now of good caliber in each of these cases This suggests that burial of only a strip of skin probably would suffice

Retraction of meatus The new meatus retracted after six first-stage Cecil operations and three Denis Browne procedures (fig 9, *a*) For practical purposes these can be considered fistulas involving the meatus If the urinary stream cannot be directed properly, reconstruction of the meatus is imperative This was done in five cases by the Thiersch-Duplay method as shown in figure 9, *b* and *c* The method was successful in four instances and failed in one

Catheters of proper caliber, more meticulous construction of the new meatus and use of reinforcing sutures when the skin and glans are approximated have prevented meatal retraction after the Cecil operation but it continues to be a problem following the Denis Browne procedure

Stricture There were 11 meatal strictures after 95 Cecil operations Most of these were the result of efforts to avoid a gaping or retracted meatus Five required meatotomy A similar meatal stenosis followed the Thiersch-Dulpay procedure in one case and was corrected by meatotomy

Three patients required internal urethrotomy All three strictures were at the site of the original hypospadiac meatus and were treated with the Otis urethrotome If adequate calibration and appropriate enlargement of the meatus had been provided *before* the first urethroplasty, urethrotomy probably would not have been necessary

Hemorrhage There was excessive bleeding from the glans after one urethro-

MANAGEMENT AND PREVENTION OF POSTOPERATIVE COMPLICATIONS

The present status of the 172 patients included in this study is summarized in table 2 Postoperative complications of varying gravity were encountered (table 3) Increased experience has shown that many of these can be prevented by appropriate precautions

Complications after operations for chordee Residual chordee Persistent angulation of the penis is the most serious aftermath of these procedures Although 19 per cent of the previous attempts to correct chordee had been unsuccessful, only one of the 107 attempts of the present series failed Residual chordee in this case was corrected at a second operation When further straightening is necessary, it is best to allow 1 year to elapse between operations

Stricture Meatal strictures developed in four patients after Z-plasty Dilatation sufficed in two cases but meatotomy was necessary in the other two If special care is taken to preserve the original meatus (as illustrated in figure 2), meatal stenosis will be avoided despite considerable freeing of the urethra If a meatal stricture should occur, it is wise to treat it adequately *before* resorting to urethroplasty

Wound separation Two patients had enough delay in wound healing to require secondary closures There was no recurrence of chordee in either case

It is apparent, therefore, that correction of chordee can be virtually devoid of complications if all constrictions are removed, if any meatus of adequate caliber is left intact and if the vascularity of the skin is not impoverished

Complications following urethroplasty—Complications after construction of the new urethra are the most disturbing and yet they are most amenable to prophylactic measures

Fistula Any complication is annoying, but fistulas have been the most disconcerting Minute ones can be just as difficult to close as large defects There is increasing evidence that fistulas can be prevented more easily than they can be repaired They occurred after 19 per cent of the Cecil operations, 44 per cent of the Browne procedures and 50 per cent of the Thiersch-Duplay operations

When performed properly the Cecil operation deliberately provides for a long tract so that it may heal spontaneously This was true in 11 of the 18 fistulas The seven that persisted were due to poor surgical judgment The urethra was freed from the scrotum too soon in two patients who had had several previous operations Portions of the urethra sloughed in each case and the operation had to be repeated When there have been numerous earlier surgical procedures the urethra should remain buried for three months In two other cases the operation failed because it was used for scrotal hypospadias and urethrourethral fistulas developed Three fistulas after burial of only a portion of the urethra could have been avoided if sufficient normal urethra had been attached to the scrotum

Three fistulas that followed the Denis Browne operation healed spontaneously but 15 persisted Surgeons more experienced with this method admit an incidence of fistula of approximately 20 per cent The operation was repeated with success in two cases and with failure in three others The Cecil method has been used to construct the remainder of the urethra in five of these patients

All defects after the Thiersch-Duplay operation were closed by the Cecil or modified Browne method

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THE ETIOLOGY AND TREATMENT OF URETHRITIS IN FEMALE PATIENTS

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In diseases of obscure etiology treatment is usually diverse and often unsatisfactory. Such is the status of urethritis in females.

This morbid condition was assumed to be caused by interstitial infection in the wall of the distal urethra. Amputation of the distal one centimeter failed to produce satisfactory results. Destruction of the entire urethral mucosa by electrosurgical methods proved even more disappointing. Further study revealed that the infection originated in the paraurethral glands. Unroofing these ducts brought encouraging results.

This report will describe a concept of the pathogenesis of urethritis and the mechanism of surgical attack on the involved paraurethral glands.

The report is based on the treatment of 171 consecutive adults with urethritis encountered in private practice.

ETIOLOGICAL CONCEPT OF URETHRITIS AND ITS COMMON COMPLICATIONS

The pathogenesis of urethritis and cystitis is illustrated diagrammatically in figure 1. In *a* the urethral gland is normal. The proximal portion of the gland is always in intimate relationship with the internal sphincter of the urethra. Normally, the mucosa possesses natural defense against the bacterial flora of the vulva. Figure 1, *b* represents the pathology of urethritis. The gland wall has been invaded by bacteria producing a low grade chronic inflammation of the entire duct. This results in scarring and partial occlusion of the gland. Symptoms of urethritis of varying degrees, arise from the presence of this inflamed gland which lies within the grasp of the sphincter. In *c* bacterial invasion of the pathologic gland by a second microbe has occurred. When these bacteria are discharged upon the urethral mucosa, acute secondary cystitis occurs, *d*. Figure 1, *e* represents failure of treatment. The gland has been only partially unroofed leaving an infected stump with similar invasive potentialities as an untreated infected gland. In *f* the stump has been destroyed producing cure.

ANATOMY

The paraurethral glands and ducts are homologues to the ducts of the prostate (fig. 2). These glands and their orifices are subject to wide variation in number and distribution. The two clinically important orifices are located in a posterolateral (5 and 7 o'clock) position just within the external meatus of the urethra. In this location the glands are submucosal, more proximally the glands become tubular and deeper in relation to the mucosa and are in intimate contact with the internal sphincter (fig. 3).

Read at annual meeting of American Urological Association, Pittsburgh, Pa., May 6-9, 1957.

plasty because the new urethra was constructed to the tip Such grandiose ambitions have been abandoned

Three hematomas in the scrotum had to be evacuated but such hematomas have been prevented in all subsequent cases by insertion of the drain at the second stage of the Cecil operation

Keloid A generous dorsal slit is said to be an essential part of the original Denis Browne operation This area usually heals promptly once the edema subsides But in one case there was painful angulation during erection and the scar had to be excised

Sacculated urethra In three cases large, dilated pouches along the urethra were excised during one of the previously described procedures All three resulted from the infamous Ombrédanne operation This procedure is mentioned only to condemn it Even if all hair follicles are destroyed it creates pouches that will not drain satisfactorily

Unrelated anomalies It has been axiomatic that other abnormalities should be suspected when one type of congenital anomaly is encountered Fourteen undescended testes, two inguinal hernias and three hydroceles were operated on successfully at the same time that chordee was corrected or when the penis was freed from the scrotum

Additional anomalies detected in this series of 172 patients included ureteropelvic obstruction, rectourethral fistula, testicular agenesia, cleft palate, absence of an ear, hammertoes, cardiac septal defects, the adrenogenital syndrome and true hermaphroditism

Comment Although the incidence of postoperative complications presumably can be reduced, it is unlikely that they can be eliminated The seriousness of such sequelae and the ease with which they can be corrected at subsequent procedures help to define the usefulness of any technique

Enthusiasm for the two-stage Cecil operation has been based on the following observations 1) it alone promises to eliminate persistent fistulas, 2) total hospitalization for both stages frequently is less than that required by one-stage operations even when they are successful, 3) a desirable type of new meatus can be created with gratifying regularity, 4) any inadequacies after the first stage usually can be corrected during the second stage, and 5) it permits more precise forecast of the amount of treatment that should be necessary in any age group

GENERAL OBSERVATIONS

Experiences with 172 hypospadiacs have emphasized that treatment of this anomaly demands infinite patience, meticulous attention to seemingly trivial details, adherence to sound surgical principles, flexibility to cope with the bizarre and the grotesque, and immunity to unwholesome rationalizations

Many different basic problems may be encountered Many types of operations are feasible and justified, none is foolproof Hypospadias continues to be both a technical and a philosophic challenge, and it is unlikely that there is any legitimate role for the occasional operator in the proper management of these anomalies

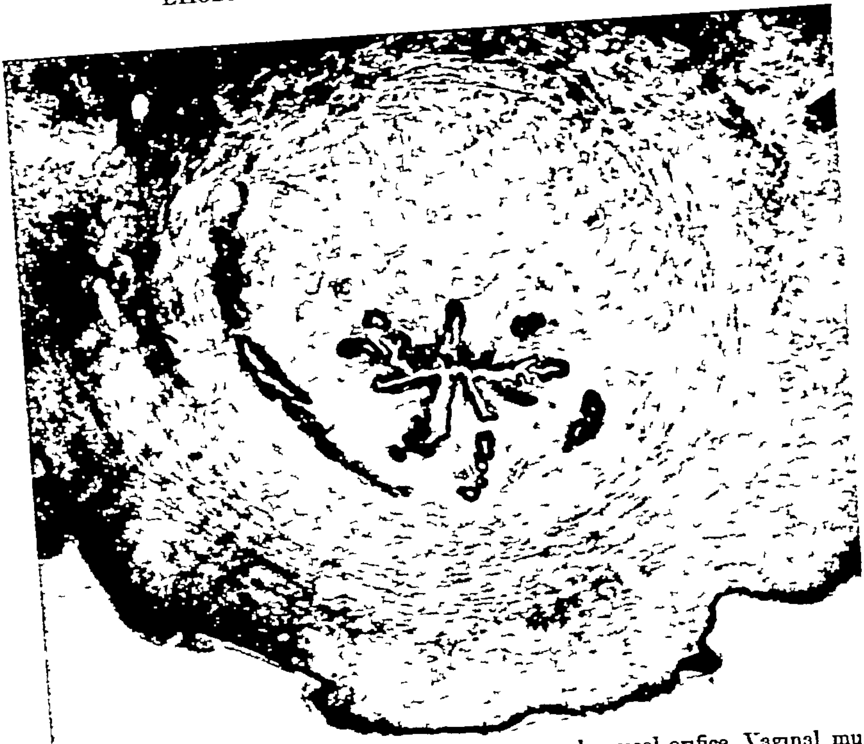

FIG 3 Cross section of urethra 0.5 cm. below internal vesical orifice Vaginal mucosa rims inferior margin of section Clinically important glands are large crescent shaped group lying deep to mucosa and in close association with internal urethral sphincter at left postero-lateral position Presence of infection in such a gland can be determined clinically by applying gentle lateral pressure upon urethra with a size 10F glass catheter at sphincter level This elicits pain or tenderness when compared with equal pressure on opposite side From Huffman (by permission of author and the C V Mosby Company)

was observed surrounding the wall of the gland in association with minute localized abscesses Inflammatory destruction of the duct wall was noted During routine autopsy studies Lintgen and Herbut[2] noted a histological inflammatory reaction of the urethra in 76 per cent of cases

The characteristic pathological lesion found in the amputated specimens of the urethra from 61 women was subepithelial focal, round cell infiltration of the glands Tissue stains for bacteria disclosed an enterococcus in the interstitial tissue (fig 4) in four specimens and in the lining epithelium in two Tissue cultures of nine specimens were positive for enterococci in five instances

METHODS OF TREATMENT

1) *Amputation of distal urethra* The initial results of amputation of the distal one centimeter of urethra indicated a 75 per cent cure rate[3] With time the number of failures increased These failures were due to persistent stumps of glands

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[2] Lintgen C and Herbut P A A clinico pathological study of 100 female urethras J Urol 55 298–305 1946

[3] Eberhart C A Hill J and Brannen J The treatment of urethritis in women a new etiological concept South Med J 46 437–442 1953

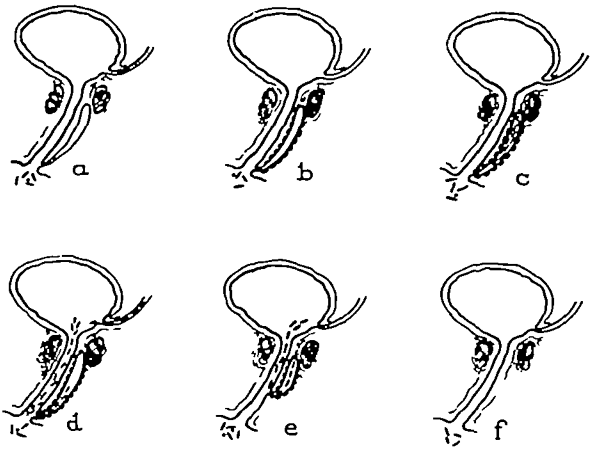

FIG 1

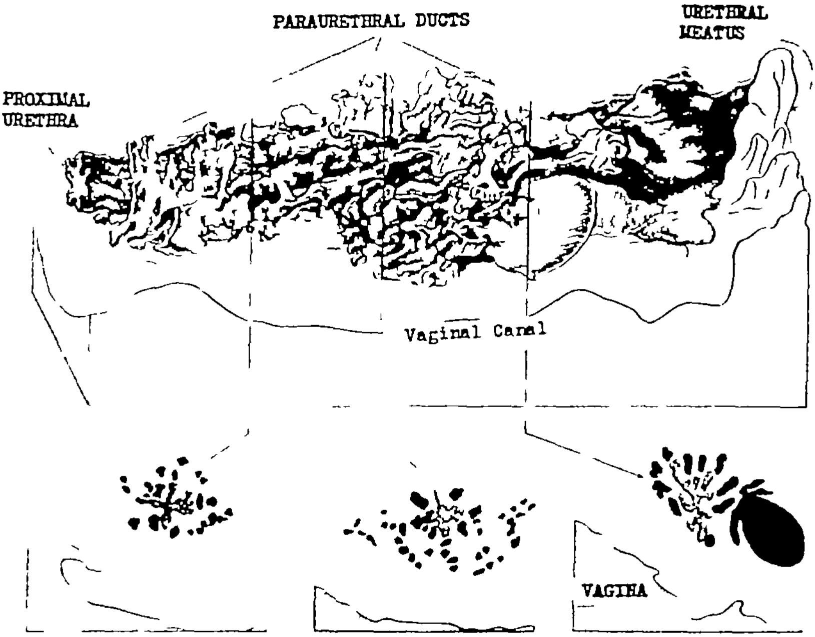

FIG 2 Wax model of urethra Right lateral view shows anatomy of urethral glands Cross sections are shown below at three levels Orifice of one duct in distal urethra is occluded producing a cyst like dilation of gland From Huffman (by permission of author and C V Mosby Company)

PATHOLOGY

Huffman[1] found cystic dilatation of the ducts and inflammatory reaction in and about the ducts and glands to be common Round cell and leukocytic infiltration

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[1] Huffman J W The detailed anatomy of the paraurethral ducts in the adult female Am J Obst and Gynec 55 86–101 1948

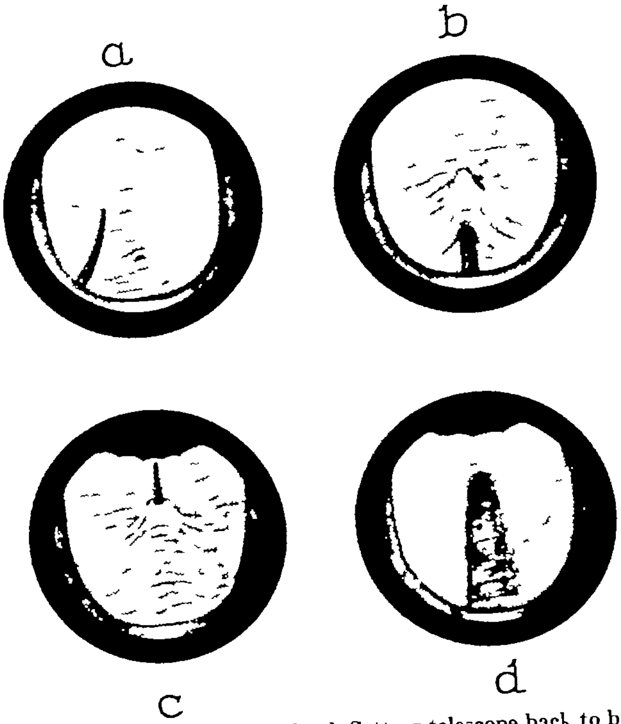

FIG 7 Showing avulsion of urethral gland Setting telescope back to bring lower lip of panendoscope sheath into view enhances visualization of urethral detail and dissipates bleeding from previous avulsion *a* Urethral gland orifice and tip of probe *b* Tenting mucosa to locate tip of probe *c* Probe pierces mucosa just below internal vesical orifice *d*, Torn furrow in mucosa following avulsion of gland

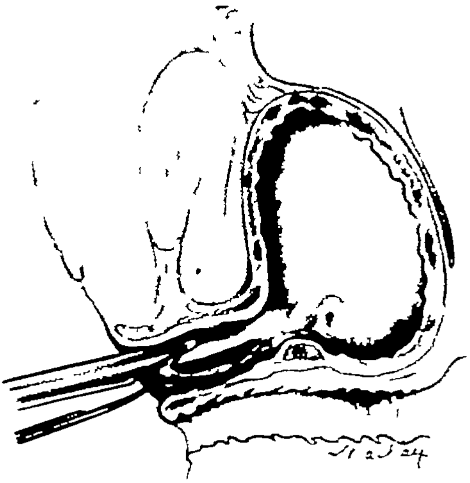

FIG 8 Tip of probe is engaged in cleft of panendoscope both being withdrawn Avulsion of a gland is almost complete

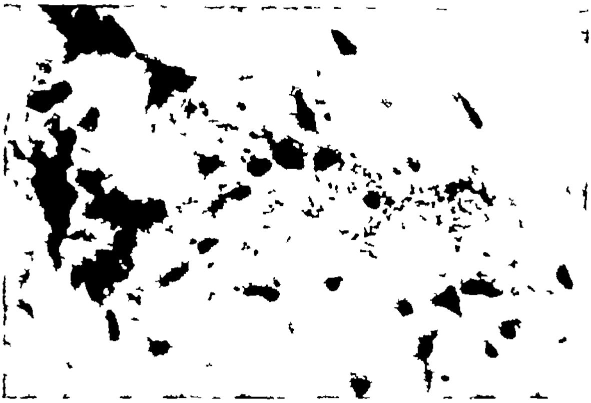

FIG 4 Oil immersion microphotograph of tissue stained by Gram's method showing interstitial bacteria which proved to be enterococcus on tissue culture A gland is seen at upper left × 970

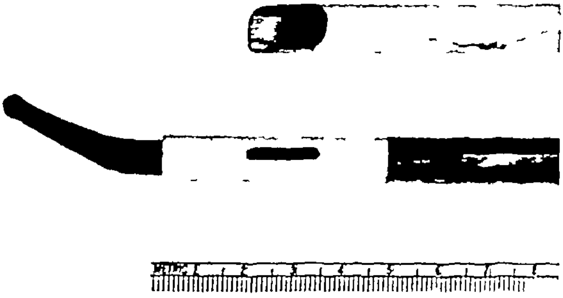

FIG 5 Shows size 28 fenestrated resectoscope sheath in relation to length of Nesbit sheath Fenestra measures 15 mm by 2 5 mm Coudé catheter serves as an obturator

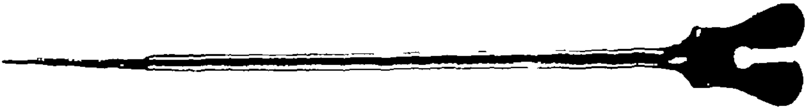

FIG 6 Probe used for avulsion of urethral glands is made by grinding a ball point groove director to a suitable size Tip is curved gently towards grooved edge

having stenotic orifices at the line of amputation In 1954 this method was abandoned

2) Cauterization of the entire urethral mucosa The mucosa throughout the length and circumference of the urethra was destroyed by continuous cauterization using a fenestrated resectoscope sheath (fig 5), a resectoscope loop and the cutting current of an electrosurgical unit with a setting at a sub cutting level[4]

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[4] Weyrauch H M, Bassett, J B and Berger M M Practical considerations in the use of high frequency currents for transurethral prostatectomy J Urol 61 371-383 1949

MORBIDITY

The ideal treatment of urethritis should be accompanied by a minimal morbidity It has been noted that in patients in whom the treatment failed, the urethritis is often accentuated Therefore, in order to determine the morbidity of avulsion, only the 49 cured cases in the avulsion group have been tabulated (table 1)

CRITERIA FOR CURE

Patients were classified as cured when asymptomatic, with no recurrences of urethritis or cystitis, and negative urine, improved when minimal subjective symptoms of urethritis persisted although urine was negative, failure when there was an estimated improvement less than 50 per cent, or a recurrent single attack of cystitis

RESULTS OF TREATMENT (TABLE 2)

When the gland is unroofed failure to produce a cure was attributed to a proximal remnant of a gland being incompletely exposed and overlying the sphincter Subsequent complete destruction of these glands resulted in cure One patient suffered a complication caused by a rupture of the fibrous sheath of the urethra 0 5 cm distal to the orifice of the bladder This resulted in partial incontinence which lasted 6 weeks

SUMMARY

Urethral glands can be demonstrated in all females who suffer from urethritis The gland orifices of greatest importance are located in the floor of the distal urethra In this area the orifices of these glands are constantly exposed to the bacterial flora of the vulva The ducts of these glands course along the length of the urethra and terminate in the region of the internal sphincter

Invasion of the urethral glands by enterococci produces urethritis Inflammatory damage causes partial occlusion of its lumen The duct is then invaded by a second micro-organism, commonly E coli When these bacteria are discharged the defense of the urethra is overwhelmed and secondary cystitis occurs

Urethritis and its secondary complications of cystitis and pyelonephritis can be arrested or cured by destruction of the pathologic gland This can be accomplished effectively as described

The author wishes to thank Dr J W Huffman and the C V Mosby Company for granting permission to reproduce the photographs in figures 2 and 3, and Dr Guy Darrell Ayer for the bacteriological studies of the urethral specimens

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This mode of treatment was also abandoned because of the low cure rate and high morbidity

3) *Avulsion or unroofing of the urethral glands* Treatment is done under general anesthesia With the irrigating fluid flowing briskly, the pan-endoscope is inserted into the distal urethra A probe (fig 6) is passed along side the instrument into the field of vision The orifices of the urethral glands have always appeared normal The probe (fig 7) is then easily inserted into the most distally placed orifice located at 5 and 7 o'clock *just within the meatus* The hidden tip of the probe can be located by depressing the handle resulting in tenting of the mucosa while advancing the panendoscope The tip of the probe is then elevated to prevent damage to the internal sphincter The overlying mucosa is pierced just distal to the internal vesical orifice The probe tip is engaged in the beak of the sheath and both are simultaneously withdrawn (fig 8) This tears a furrow in the mucosa Usually it is necessary to avulse only the two glands located at 5 and 7 o'clock Postoperatively, there is a marked tendency for the gland to heal by coalescence of the incised edges, more particularly at the proximal end For this reason the torn edges of the mucosa are trimmed away employing the fenestrated sheath (fig 9) In addition a 26-30F Foley catheter, left indwelling for four days, further prevents the reformation of the roof of the duct

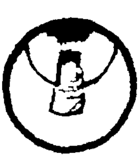

FIG 9 Endoscopic view of fenestrated sheath showing torn edge of mucosa being trimmed using a 10 gauge loop Arterial bleeders are easily located and coagulated

TABLE 1

Morbidity	Degree	Number of Patients	Per cent
No symptoms	0	23	46
Dysuria up to 2 weeks, no narcotics	1+	15	31
Dysuria up to 2 weeks, with narcotics	2+	8	17
Dysuria beyond 2 weeks, with narcotics	3+	2	4
Dysuria, catheter and narcotics required	4+	1	2
Total		49	100

TABLE 2 *Results of treatment*

Number of Patients	Method	Time Followed	Cured	*Improved*	*Failed*
61	Amputation	36 months	26 (43%)	8 (13%)	*27 (44%)*
23	Cauterization	19 months	5 (22%)	*7 (30%)*	*11 (48%)*
87	Avulsion	*13 months*	49 (56%)	*28 (32%)*	*10 (12%)*

caused by the injection of some such substance as bichloride of mercury or 1 1000 acriflavine solution (where the urethra has been kept filled with the solution even under gentle pressure for even fairly short periods)

ETIOLOGY OF ACUTE POST-TRANSURETHRAL RESECTION URETHRITIS

It can be seen from the following description of the technique which I have employed for many years for the transurethral resection operations and the methods employed for the sterilization of the genitalia and instruments, as well as the other procedures, it is unlikely that the preoperative, operative, or postoperative measures are the principal causes of the acute urethritis

In the many years that I have been doing transurethral resections I have varied my technique very little The Davis-Bovie electrosurgical unit (not the A G unit) has been used with the cutting current set at 55 or 60, rarely 65, and the McCarthy electrotome made by American Cystoscope Makers, Inc Some years ago I began using glass instead of bakelite sheaths and a little later melamine sheaths also For many years all my instruments were sterilized by immersion in 10 per cent formalin solution, but for several years I have used a solution of A C M I urolocide in which the instruments and cords have been soaked for never less than one hour As an irrigation I used sterile distilled water until about three or four years ago when I changed to cytal solution

The Liebel-Flarsheim electrosurgical units have been thoroughly checked by a factory representative He found nothing wrong I tested the sheaths, which I had been using, by clipping the wire of the inactive electrode to the tip of the sheath and, with the sheath submerged, passing the active electrode along it to within three or four millimeters of the inactive electrode There was no visible evidence of activity of the electric current

The patients have been shaved and cleaned in their rooms, and as soon as they were put on the operating table I have tried to sterilize the urethra as far as possible by injecting 1 1000 acriflavine into the urethra a couple of times Retention of sufficient acriflavine in the urethra to cause strictures has been prevented by careful compression along the urethra before the electrotome sheath was inserted Tincture of zephiran solution has been used for sterilizing the skin of the penis, pubes, and scrotum The drapes have been towels and a large sheet

The anesthetic has usually been spinal (not a high one) reinforced when necessary by gas-oxygen or pentothal sodium The preanesthetic hypodermics have for years been seven grains of sodium luminal followed by pantopon or demerol and atropine

The retention urethral catheters have always been sterilized by boiling for thirty to forty minutes In the past few months they have been autoclaved at 50 pounds pressure for 15 minutes If the urethritis has been caused by inadequate sterilization of the catheters or instruments it certainly would have appeared years ago instead of just last year

After the fourth case of acute urethritis occurred, everything in the transurethral resection operating room was autoclaved which could be sterilized in that manner, and the room was thoroughly cleaned, sealed, and sterilized for 24 hours

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SEVERE ACUTE URETHRITIS FOLLOWING TRANSURETHRAL PROSTATIC RESECTION

MONTAGUE L BOYD

From April 1956 to December 1957 I had five patients who acquired acu urethritis after transurethral resections, a complication of the operation nev encountered by me previously It is a severe inflammatory process accompanie by extensive stricture formation necessitating treatment by urethral dilatatio with sounds

On the first postoperative day there is edema of the meatus and of the glan, and at times, some edema of the prepuce Some urethral discharge occurs about the catheter, when, on the fourth day, the catheter is removed the urethral edema, with the discharge drying at the meatus, may seal up the urethra At the first few voidings after the removal of the catheter the urine is passed fairly well, but within twelve to twenty-four hours a definite diminution occurs in the size and force of the stream and voiding is frequent and painful In two cases I have had to replace the urethral catheter and in two a 24F bougie à boule was tight in the urethra, its passage was painful and followed by a good deal of bleeding

DIFFERENTIAL DIAGNOSIS

This type of urethritis should be distinguished from the ordinary slight urethritis which sometimes occurs after urethral trauma and at times, in so-called allergic patients, follows catheterization While the severity of the inflammation in these cases varies, and at times may be marked, I have seen no subsequent stricture development

Nor is it the urethritis which follows transurethral resection where delayed stricture formation occurs, in such cases the symptoms of acute urethritis are absent This type of complication has happened *infrequently* in my cases of transurethral resection, and I have always thought that the strictures resulted from some localized urethritis existing prior to the operation, or to a narrowing of the meatus or of the pendulous urethra, changes which were inflammatory or congenital and were marked enough to cause inadequate circulation in the abnormal parts of the urethra during the time that the sheath of the resectoscope was in it In none of those cases has the patient had acute urethritis symptoms and there has not been such evident trouble in voiding immediately after operation The strictures were discovered at routine checkups of patients several weeks after operation

The urethritis of the acute nonspecific type, not infrequently seen by urologists, where there is a more or less profuse purulent urethral discharge, is not followed by urethral strictures, and almost all of such cases have a pretty marked prostatitis and posterior urethritis from which the symptoms arise

In the past the only strictures which I have seen following acute urethritis have been from acute gonorrheal urethritis or from the severer cases of urethritis

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Read at annual meeting of the American Association of Genito Urinary Surgeons Hot Springs, Va , May 1-3, 1957 the urethritis did not always occur following transurethral resection, nor did it occur in any of my nonoperative cases where retention catheters were used However, I have been told (personal communication)* that a neurosurgeon had several cases of rather severe acute urethritis from using a retention catheter after spinal operations, and only a month ago I saw one such case 24 hours after an A C M I catheter had been inserted in which there was edema of the meatus, the glans, and the prepuce

Another urologist† had two cases of acute urethritis where the same make of retention catheters was used, one following a retropubic bladder operation and the other after operation on a perineal abscess In early April 1957 he performed two transurethral resections the same day, using a Bardex Foley in one case and an A C M I in the other, the patient who had the A C M I catheter had acute urethritis He has had altogether seven or eight cases, most of them after transurethral resections

To test for skin sensitivity to the catheters I cut small pieces of both Bardex and A.C M I catheters and fastened them to the inner thighs in two of the patients who had had acute urethritis The pieces were covered with adhesive plaster, which in turn was covered with collodion, and they were left on four days on one patient and six or seven on the other, without the slightest sign of redness under the rubber

I have talked with Mr Kleine, the American Cystoscope Makers, Inc representative in our territory, and recently to Mr Frederick J Wallace They both tell me that they make their own catheters at A C M I and have in no way changed the composition of the rubber in the catheter and, furthermore, that A C M I has had no report from anyone else concerning urethritis from the catheters although they have sold many hundred catheters I do not see, in consideration of this information, how it could be the type of catheter which is the causative factor

On December 27, 1956 I made a report of the occurrence of this complication in an Urologists' Correspondence Club letter, and I have had only two replies, one from an urologist who had seen only one case and another‡ from an urologist who reported that five of his cases had this type of urethritis, four after transurethral resections and one after a suprapubic prostatectomy He writes me that the retention catheters were latex Foley catheters made by A C M I

It seems improbable that the acute urethritis results from a sensitivity to any of the antibiotics The third and fifth of these five cases had no sensitivity to drugs The first and fourth had had skin eruptions from penicillin but received none at or after operation, the second case had a history of skin eruption from sulfonamides and, of course, was given none All of the patients received some antibiotics after operation case 1, terramycin and chloromycetin, case 2, combiotic furadantin, and mysteclin at different times, case 3, combiotic and chloromycetin, case 4, chloromycetin, case 5, mysteclin In none of the patients with formaldehyde But still the complication has continued in spite of these precautions, and even when, about the last of March 1957, we moved to the newly completed Piedmont Hospital, one case of acute urethritis followed a transurethral resection, and one case of severe urethritis occurred when a retention catheter was placed in the urethra of a patient following a spinal operation

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* Dr Homer Swanson

† Dr Samuel S Ambrose Atlanta, Ga

‡ Dr Arthur J B Butt Pensacola, Fla

For lubrication of the electrotome I have used A C M I jel for many years, frequently removing and relubricating the sheath during the operation The long continued use of this lubricant without acute urethritis would seem to eliminate it as a cause in my cases, and another urologist has had acute urethritis occur although he used mineral oil and vaseline for lubrication of the sheath The inactive electrode under the patient has either been wet with water or had K Y jelly applied Of course, batteries have been employed for lighting the lamps on the telescopes

Urethral trauma resulting from the urethrotome in a narrowed urethra is not a likely cause On all of the five patients I had passed a 28 or 29F bougie à boule easily through the meatus, and to the external sphincter, before I operated upon them and on the last patient I passed a 32F bougie à boule without encountering any resistance In only one case was there any evidence of preoperative urethritis That was the fourth case where the passage of a 29F bougie à boule resulted in a slight bleeding from the urethra but no sign of tightness of the urethra was found

I have been corresponding with Dr Hjalmar Carlson of Kansas City concerning the etiology of post-transurethral resection strictures He stated in an Urologists' Letter Club letter of January 10, 1955 that strictures invariably occurred as the result of using the same electrotome sheath more than 75 times and if he changed to a new sheath no strictures occurred I cannot be sure that he and I are discussing the same complication His letters do not seem to indicate that his patients had acute urethritis As I have pointed out above, the usual post-transurethral resection stricture develops without all the severe symptoms which occur in these cases of acute urethritis I have not counted the number of times that I have used my different sheaths but I am sure that they have not been used more than thirty or forty times since they were new However, I have now only new sheaths

For the postoperative retention catheter I used for many years a straight red rubber urethral catheter but rarely a size larger than 18F When the Foley catheter came along I began using a 20 or 22F Foley latex catheter with a 30 cc bag, usually putting only 12 to 15 cc of water in the bag Both Bardex and A C M I catheters were used without discrimination until the early part of 1956

The trauma from the postoperative retention catheters in my cases has been the same for years without producing a single case of acute urethritis In the first case having this acute urethritis a 22F "Wheeler" (Bardex) Foley catheter was used Immediately after that I began using the new A C M I Foley catheter (which was put on the market at about that time) because of the reaction with the Wheeler catheter and because the new A C M I catheter had a much larger lumen than any of the other Foley catheters Although we began using the new A C M I catheters exclusively at the Piedmont Hospital it must be noted that hypertrophy The bladder neck elevation and fixation made it difficult to pass the sheath of the electrotome Microscopic sections of the resected tissue showed a very few quite small areas of carcinoma (confirmed by the Armed Forces Institute of Pathology) He had no postoperative elevation of temperature but the urethral obstruction, following the removal of the retention catheter, was the most marked of any of the cases Voiding was frequent, difficult, and painful Instrumentation without general anesthesia was almost unbearable The catheter was replaced several times for one, two, or three days at a time Subsequently, since I had to administer a general anesthetic to dilate his urethra, I did an internal urethrotomy (about three months after the transurethral resection) He has been taking stilbestrol continuously since the carcinoma was reported to have been found

Since endoscopy, cystoscopy, and rectal palpation at the time of the internal urethrotomy showed no further evidence of carcinoma I sent him, for the sake of thoroughness, to Dr Charles Higgins for consultation At the Cleveland Clinic a transurethral biopsy of the bladder neck and remaining prostate tissues was done without discovering any carcinoma

Case 5 H J D , 59, married (Piedmont Hospital No 168820), was operated upon December 21, 1956 He was a man upon whom I had done a transurethral resection in July 1948 He returned in 1956 with chronic prostatitis, which was very resistant to treatment and, also, a recurrent benign prostatic hypertrophy Before the transurethral resection a 32F bougie à boule was passed quite easily through the urethra

He had elevation of temperature to 100F the day of and the day after operation, and a great deal of pain from the acute urethritis But I think that he was more sensitive to pain than usual I had to dilate his urethra under a general anesthetic a number of times, after which he seemed quite well

CONCLUSIONS

Five cases are reported of severe acute urethritis following transurethral resection There is almost immediate visible edema of the meatus and even in some cases of the glans and of the skin about the coronary sulcus Urination becomes painful and difficult once the retention catheter is removed and the caliber of the urethra is considerably reduced All the patients have acquired extensive fibrous strictures of the pendulous urethra which have required months of urethral dilatation with sounds

Careful consideration of most, if not all, of the causes for such a complication is discussed without any conclusion being reached as to the etiology

It is made clear that this is a severe complication which should receive serious consideration if evidence of its continued occurrence accumulates

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was there evidence of skin eruption or gastrointestinal upset, except in the first case where the dermatitis on the hands had been present before operation

Cultures of the urethral discharge were unfortunately not made Perhaps something could be learned from cultures although the urethral discharge was not profuse Protecting the meatus from contamination by sterile dressings put on over the glans penis at the end of the operation might offer a better chance of getting an uncontaminated culture Accurate determination of the kind of organism found in the urethra after the catheter is removed is made difficult because all patients having retention catheters after transurethral resection have, invariably, infected bladders in spite of the administration of chemotherapeutics and antibiotics, so that when the catheter is removed and the patient voids, the urethra is, of course, contaminated by the bacteria in the urine and, with the stricture formation which is present, there is a tendency for the retention of urine in the urethra to exist

CASE REPORTS

Case 1 The first patient having this complication of acute urethritis was W H M (Piedmont Hospital No 163599) 57, married He had been treated for some years for an "allergic" dermatitis on his hands, which was still present, and there was a history of his having had a skin eruption from penicillin He had a benign prostatic hyperplasia and also a chronic prostatitis and a 22F "Wheeler" (Bardex) Foley retention catheter was used On the first and second postoperative days he had elevation of temperature to 101 (which is in my experience unusual for transurethral patients) but none thereafter As this was the first time I had ever seen the complication of severe acute urethritis I thought it was an allergic reaction and requested his general medical doctor to start treating him for allergy He had a good deal of discomfort on voiding and did not void very well He went home on the sixth postoperative day, but had so much trouble that he came back the same day, and I found that an 18F catheter was tight in the pendulous urethra and that the residual urine was 300 cc He improved slowly and went home again on the twelfth day The urethra subsequently was gradually dilated with sounds, at increasingly longer intervals, to 32F for about four months

Case 2 J J J (Piedmont Hospital No 165032) aged 52, married, had a long standing bladder neck obstruction due essentially, I believe, to chronic prostatitis and perhaps some congenital bladder neck changes, and he also had some early benign prostatic hypertrophy I had treated him earlier for chronic prostatitis and chronic seminal vesiculitis He had little or no postoperative fever and his postoperative history was much the same as the others

Case 3 J M F, aged 61, married (Piedmont Hospital No 167705), had early benign prostatic hypertrophy, and elevation of temperature after operation to 99 8F at most for a couple of days, and his postoperative history was much the same as the others

Case 4 T C L, 75, widowed (Piedmont Hospital No 168313), had a bladder neck fixation due seemingly to chronic prostatitis, and a small benign prostatic

The edema included a portion of the foreskin on the right side of the frenulum There was no ulceration or abrasion noted

Laboratory studies were as follows red blood cell count 4 0 million, white blood cell count 8 0 thousand, hemoglobin 11 5 grams, urinalysis was negative for albumin and sugar, no cellular debris was noted in the centrifuged specimen Sedimentation rate was 7 mm in one hour, VDRL and Kolmer agglutination tests were negative A routine chest x-ray was normal An electrocardiogram was normal

A provisional diagnosis of thrombophlebitis of a dorsal vein of the penis was made

Treatment with phenylbutazone (butazolidin) 100 mg 4 times a day was started on the date of examination and continued for 10 days The edema and tenderness subsided markedly within 48 hours of treatment, and examination on the tenth day revealed a normal penis with no evidence of edema and no palpable or tender venous mass

Followup examinations have been made at monthly intervals and there has been no recurrence

COMMENT AND SUMMARY

A case of thrombophlebitis of a dorsal vein of the penis has been presented Treatment with phenylbutazone (butazolidin) was entirely satisfactory The etiology of the condition is undetermined No similar case has been found in the literature

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THROMBOPHLEBITIS OF A DORSAL VEIN OF THE PENIS REPORT OF A CASE TREATED BY PHENYLBUTAZONE (BUTAZOLIDIN)

JOHN D HELM, JR AND IAN G HODGE
From Lancaster General Hospital, Lancaster, Pa

A review of the literature failed to disclose a report of a case of thrombophlebitis of the veins of the penis Localized thrombophlebitis is uncommon except in the legs and is even less common in an ambulatory, otherwise healthy patient

The use of phenylbutazone has been described in many inflammatory states[1] Stein and Rose[2] described its efficacy in superficial thrombophlebitis Its pharmocology, dosage, and toxicity have been reported[3]

CASE REPORT

A 29-year-old white man was first seen on August 27, 1956, complaining of a localized swelling and associated pain along the dorsum of the penis This symptom recurred each morning He had noted a firm cord-like structure extending along the dorsal aspect of the penis in the region of the swelling whenever such swelling was present There seemed to be some association between the swelling and a full bladder and occasionally the swelling subsided after voiding There was no relationship between the swelling and sexual relations His only other complaint was vague low back pain, present particularly in the early morning His past medical history was negative, except for "inflammatory rheumatism" as a child Family history was non-contributory Physical examination height 5 feet 11 inches, weight 169 pounds, blood pressure systolic 124 mm , diastolic 72 mm Well fitted, partial dentures were noted Both the lungs and the heart were essentially normal On abdominal examination no areas of localized tenderness and no palpable masses were noted On examination of the external genitalia, at the time of his initial examination, nothing significant could be detected On February 15, 1957, on a return visit, examination of the penis revealed a hard, tender vein extending along the dorsal aspect The vein was readily visible as it traversed the coronal sulcus The overlying skin in the region of this vein was slightly inflamed and surrounded by edematous tissue

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Steinbrocker, O , Berkowitz, S , Ehrlich, M , Elkind, M and Carp, S Phenylbutazone therapy of arthritis and other painful musculoskeletal disorders J A M A , **150** 1087, 1952

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[3] Stephens, C A L , Jr , Yeoman, E E , Holbrook, W P , Hill, D F and Goodin W C Benefits and toxicity of phenylbutazone (butazolidin) in rheumatoid arthritis J A M A , **150** 1084, 1952
Hinz, C , Lamont Havens, R W , Cominsky, B and Gaines, L M Agranulocytosis following use of phenylbutazone (butazolidin), report of a case J A M A , **151** 38 1953
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CYSTS OF THE PROSTATIC UTRICLE (MÜLLERIAN DUCT CYSTS) REPORT OF TWO CASES IN CHILDREN, EACH CONTAINING CALCULI, CURED BY RETROPUBIC OPERATION

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An increasing number of papers in the literature, relating to disorders of the remnants of the mullerian duct system in males, attests to the clinical importance of this subject The subject has been well reviewed by Moore and Howe in 1953, and by Slocum in 1954, who give an extensive bibliography The latter author states that 49 cases of mullerian duct cysts have been reported Undoubtedly the incidence of such cysts, however, is more common than the literature would indicate, as borne out by the fact that we have seen personally several presented at informal pyelogram conferences at urologic seminars and sectional meetings

The purpose of this paper is to present two cases of cyst of the utricle occurring in children, each containing calculi, and to describe a comparatively simple surgical technique for correction of the lesion when the cyst is not unduly large

EMBRYOLOGY

It is generally accepted that the müllerian duct system, which arises during the undifferentiated stages of development of the human embryo, gives rise to the fallopian tubes, uterus, and upper vagina in the female, whereas, in the male the mullerian ducts regress except for the cranial ends which persist as the appendices testes and the joined caudal ends which persist as the prostatic utricle or uterus masculinus (fig 1) This is the depression which is noted in the midline on the verumontanum between the openings of the ejaculatory ducts customarily seen on routine panendoscopy Failure of the normal regression may give rise to a cystic structure of varying size Slocum lists persistence of mullerian duct structures on a genetic or hormonal basis and abscess formation in the prostatic utricle as possible etiologic possibilities in the formation of these cysts

CLINICAL PICTURE

Symptoms vary tremendously depending upon the size of the cyst and the presence or absence of infection In some reports no symptoms have been noted, a midline cystic mass in the region of the prostate being detected only on rectal examination More commonly, however, disturbances of micturition, perineal discomfort, and bloody or watery urethral discharge have been reported A very large cyst may be felt on abdominal palpation, and is usually considered to be a full bladder until its persistence after catheterization is noted The most helpful diagnostic measure is radiographic demonstration of the cyst after injection of

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Read at annual meeting of the American Association of Genito Urinary Surgeons, Hot Springs Va , May 1-3 1957

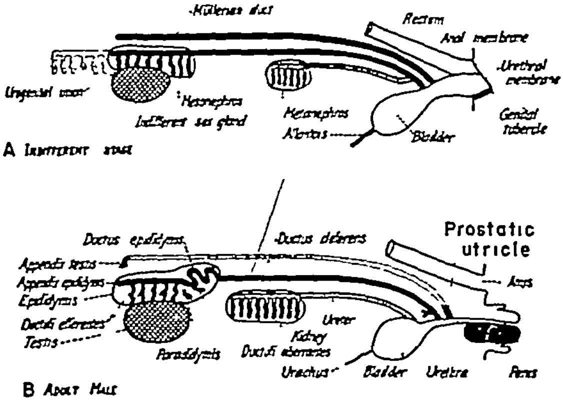

FIG 1 Diagram showing male and female genital duct systems as present in undifferentiated stage and in fully developed male (From Dodds, G S Essentials of Human Embryology, 3d ed New York J Wiley & Sons, 1946)

radiopaque dye by means of catheterization of the utricle or by perineal puncture The cyst contents have been variously described as serous, mucoid, purulent, or hemorrhagic Demonstration of subvesical location of calculi on oblique and lateral cystograms is suggestive evidence of a müllerian duct cyst

TREATMENT

Depending upon the circumstances, rectal massage, conservative drainage by catheterization of the utricle, or perineal, suprapubic, or retropubic surgical excision has been carried out in the cases reported in the literature In general the smaller cysts have been approached by the perineum while the larger ones, which have presented abdominally, have been approached from above Due to the intimate association of the cyst wall with the undersurface of the bladder, prostate and rectum, the majority of the surgically treated patients have presented difficult technical problems

The technique carried out in our two cases, namely, saucerization of the cyst through the retropubic transvesical approach would seem preferable where the size of the cyst would permit this The details of the operation are described in the first case report below and are illustrated in figures 3 and 4

CASE REPORTS

Case 1 D M & S Clinic No C 7591 An 18-month-old white male infant was seen on April 17, 1952 with a history of frequency, dysuria, bloody urine of 24 hours' duration Physical examination was normal A plain x-ray film and a cystogram were normal Cystoscopy with the No 14 McCarthy miniature cystoscope, carried out under general anesthesia, disclosed diffuse acute hemorrhagic cystitis The bladder neck was considered normal Bilateral retrograde pyelograms showed mild right and moderate left hydronephrosis, both due to slight ureteropelvic junction obstruction The symptoms and the urine cleared rapidly on chemotherapy so that it was felt proper simply to observe the child inasmuch as the upper urinary tract changes were not sufficiently marked to warrant pyeloplasty

A similar minor attack occurred a few months later but cystoscopy and pyelograms showed no significant change and it was again decided to observe the child

No further symptoms occurred until April 25, 1955 at which time the boy was 4½ years of age The child had been well over the preceding three years until a few days before the current admission when he had experienced considerable difficulty voiding, associated with low abdominal pain

An x-ray (fig 2, *A*) now showed a cluster of 14 small stones behind the symphysis, and the cystogram showed these calcific shadows to be subvesical in location (fig 2, *B* and *C*) Excretory urography demonstrated slight hydronephrosis on both sides attributable to coincidental ureteropelvic junction obstruction From the position of the stones it was surmised that they might well lie within a cyst of the utricle Cystoscopy under general anesthesia now showed a definite contracture of the bladder neck with elevation of the floor, but no stones were seen within the bladder or prostatic urethra There was questionable crepitation to the rectal examining finger

Open operation was carried out on April 25, 1955 (figs 3 and 4) Through a transverse suprapubic incision, the anterior surface of the bladder and prostatic urethra were exposed by the retropubic approach The bladder was opened and found to be thickened and trabeculated There was a definite rim of tissue at the bad der neck No stones lay within the bladder The incision was then extended longitudinally through the roof of the prostatic urethra With the finger of an assistant in the rectum, the obstructing tissue at the posterior lip of the bladder neck was excised after the method of Burns Palpation then revealed the calculi lying in a cavity about 1 cm in diameter beneath the prostatic urethra and trigone This cavity was opened and 14 stones measuring from 1 to 2 mm in diameter extracted The cavity was completely saucerized by excising its roof and suturing its lining mucous membrane to the mucous membrane of the trigone The verumontanum could not be identified The opening in the bladder and anterior prostatic urethra was closed, leaving a No 14 Foley catheter indwelling Exposure was excellent throughout the procedure The remainder of the wound was closed in layers with Penrose drainage

On analysis the stones were found to be composed of apatite (calcium phosphate) Histologic examination of the cyst lining showed "squamous metaplasia "

Convalescence was uneventful, the catheter being removed on the seventh day Following this the patient voided with a strong forceful stream and with excellent control The mother stated that in retrospect it had never been forceful preoperatively Two months after operation, a checkup cystoscopy was carried out The bladder neck was funnel-shaped, and the original remnant of the cyst had shrunken and become incorporated in the bladder neck

Six months later the child was seen because of an acute attack of pain in the right renal area Excretory urography showed progression of the right hydronephrosis, so ureteropyeloplasty on the right was carried out on November 15, and on April 6, 1956 a similar procedure was done on the left Convalescence

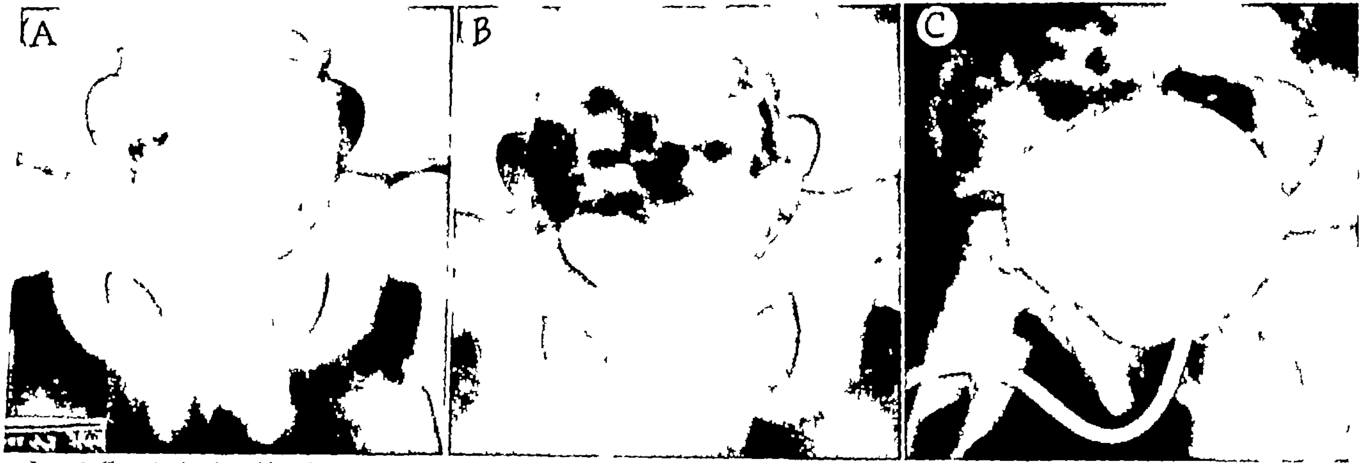

Fig 2 Case 1 *A*, plain film showing nest of small calculi which on anterior posterior and oblique cystograms (*B* and *C*) are seen to lie below and behind bladder neck

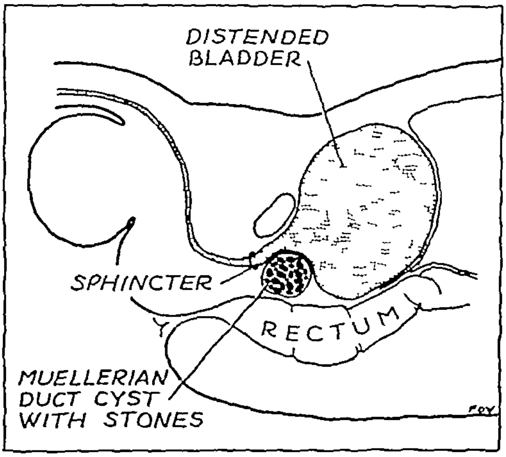

FIG 3 Diagram of findings in case 1

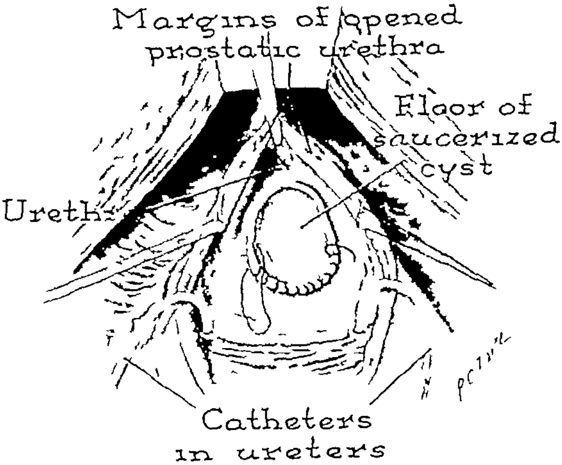

FIG 4 Drawing showing operative approach and appearance after saucerization of the cyst

from both operations was smooth Postoperative urograms showed satisfactory results

Comment Several features seem worthy of comment in this case The most striking is the development of multiple stones within a cyst of the utricle during the three-year interval that the child was under observation Surgical technique was gratifyingly simple and satisfactory, and apparently has resulted in a permanent cure In retrospect the cyst of the utricle was causing bladder neck obstruction before the final episode The associated bilateral hydronephrosis, due to ureteropelvic obstruction, was apparently a coincidental finding unrelated to the lower tract disease

Case 2 W T S, Texas Children's Hospital No 29,994 A five-year-old child had symptoms of dysuria, suprapubic pain, pyuria and frequency and urgency amounting to incontinence of two months' duration When first seen in January

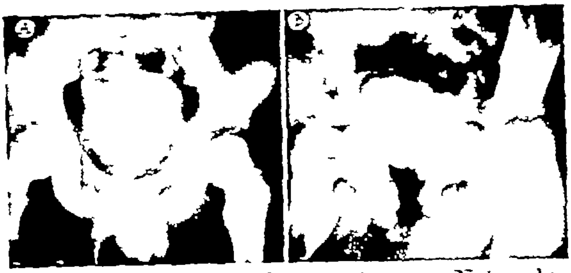

FIG 5 Case 2 Anteroposterior and oblique cystograms Note subvesical location of calculi subsequently found to lie in cyst of utricle

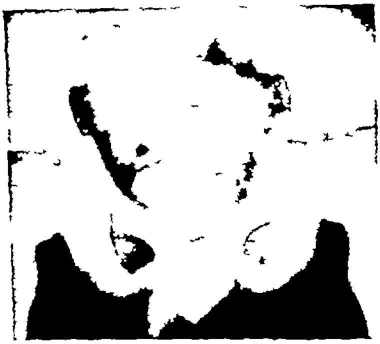

FIG 6 Stones have reformed in case 2 two upper ones being in bladder and lower ones in cystic cavity left behind at first operation

1955 general physical examination was normal Rectal examination revealed a tender hard mass, about the size of an English walnut in the region of the prostate in the midline All appropriate laboratory studies were within normal limits except for gross and microscopic pyuria with Proteus on culture A plain x-ray excretory urogram and cystogram (fig 5 *A* and *B*) showed one stone lying within the bladder and one or more stones interpreted as lying within the region of the prostate The upper urinary tract was normal Cystoscopy was not entirely satisfactory but a stone was seen in the bladder and a mass indented the floor of the prostatic urethra which grated as the cystoscope was passed over it On February 1 1955 through a midline suprapubic incision, the bladder was opened and the bladder calculus was removed, after which an additional stone was seen to have one end projecting into the urethral lumen, and the remaining stones lying in a pocket behind and above the prostate These were fragmented in efforts at removal but as near as could be told all were removed No attempt was made to saucerize or obliterate the cavity and the bladder was closed about a suprapubic tube

The immediate convalescence was smooth but two months later because of persistent pyuria and symptoms of cystitis urethrography and cystoscopy were repeated This revealed a calcification lying posterior to the prostatic urethra which represented a fragment remaining from the first operation Treatment was directed at medical attempts to clear up the urinary tract infection However the child did rather poorly, and was readmitted in January 1956

Cystoscopy on this admission showed a large diverticulum-like cavity communicating with the floor of the prostatic urethra, which contained two large calculi Additional stones were noted within the bladder itself (fig 6) The bladder neck was narrow and contracted

On reviewing the entire problem, it was concluded that the primary lesion here was a cyst of the utricle with recurrent calculus formation Accordingly, a retropubic saucerization operation was carried out The bladder was opened and the bladder calculi removed The floor of the bladder neck was excised and the underlying prostatic urethral diverticulum was unroofed and the calculi therein removed The cavity was saucerized by the method described above, following which the patient made a satisfactory convalescence The urine became clear and bladder function returned to normal

Unfortunately the child was lost to followup for one year and on return was found to have a stricture at the bladder neck with stones again in the bladder A Bradford Young enlargement of the bladder outlet was accomplished at which time the previously saucerized cyst had not reformed A postoperative urethrogram showed a normal prostatic urethra and bladder neck

SUMMARY

Two cases of children with utricle cysts containing calculi, were operated on by retropubic saucerization technique

The technique consisted essentially of exposing the anterior surface of the bladder and prostatic urethra through the conventional retropubic approach, just as when one does a Burns or Bradford Young bladder neck revision After opening the bladder low down and extending the incision into the prostatic urethra, visualization was excellent, and the cyst was deroofed, the calculi extracted and the margins of the cyst lining, forming the floor of the cyst, were sutured to the adjacent mucous membrane of the normal prostatic urethra and trigone Care was taken in each instance that saucerization was complete and no "pockets" remained Bladder neck contracture was present in both instances, and this was corrected simultaneously with the saucerization of the cyst Indwelling urethral catheter drainage for five to seven days with routine wound closure completed the procedure

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GENITOURINARY BLASTOMYCOSIS: CASE REPORT AND REVIEW OF LITERATURE

DONALD ROLNICK AND GEORGE O. BAUMRUCKER

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H. C. H., a 53-year-old white man, was well until March 1952, when osteomyelitis of the right foot developed. The osteomyelitis eventually required a right below-knee amputation which was performed at another hospital in April 1952. Pathological report of the amputated extremity revealed blastomycosis of the bones of the right foot. On May 30, 1952, he was admitted to Hines Veterans Administration Hospital with a two-day history of acute urinary retention. He gave no history of previous urinary complaints.

Chest x-ray on admission was consistent with blastomycotic involvement of the lungs. Shortly thereafter the patient became febrile and multiple cutaneous lesions developed. The diagnosis of blastomycosis was confirmed by prostatic smear and culture, and by biopsy of one of the cutaneous lesions. Three 24-hour urine specimens were negative for blastomycosis on smear and culture. An intravenous pyelogram was normal. Cystoscopy revealed early hypertrophy and marked inflammation of the prostate gland.

The patient was given a course of stilbamidine therapy in conjunction with iodides. On this regimen his cutaneous and pulmonary lesions cleared. At the time of discharge on December 23, 1952, the patient had no urinary complaints and prostatic smears were negative for blastomycosis (Cummins, Bairstow and Baker).

Following discharge he was seen at three-month intervals until January 1956. During this period he had no genitourinary complaints and prostatic smears were negative for blastomycosis. Chest x-rays were normal and there were no cutaneous lesions.

He was readmitted to Hines Veterans Administration Hospital on April 24, 1956, with a two-day history of marked dysuria. The patient gave a history of left epididymitis in March 1956 which had responded to conservative management. There were no respiratory complaints and no history of cutaneous lesions.

Temperature was 100.0F. Physical examination was essentially negative except for an old right below-knee amputation, a firm, nodular, nontender enlargement of the left epididymis, and a prostate which was soft, boggy, tender, nonnodular and not enlarged. The lungs were clear. There were no cutaneous lesions.

At the time of admission a greenish-yellow purulent material was expressed from the prostate on massage. Microscopic examination of this prostatic secretion revealed the presence of small, round, double refractile bodies typical of blastomycosis. Three separate prostatic smears revealed the Blastomyces dermatitidis organism, but cultures of all three smears were negative for blastomycosis. Three 24-hour urine specimens were obtained for blastomycosis smear and culture. One of these was positive for blastomycosis. Intravenous pyelogram revealed mild blunting of the superior calyx of the right kidney. Retrograde pyelography was performed at which time urine specimens were obtained from both kidneys The urine from both kidneys was negative for blastomycosis as well as being sterile on routine culture Bladder urine culture revealed hemolytic Staphylococcus aureus, coagulase negative Blood count, serology, and liver profile were all essentially normal There was a moderate leukocytosis with a normal differential Urinalysis revealed 20 white blood cells per high power field Chest x-ray revealed costophrenic angle pleural thickening, but otherwise was normal Electrocardiogram was normal Skin tests for blastomycosis 1 100 and coccidioidomycosis 1 100 were negative

The patient was placed on antibiotics with little relief of his urinary complaints A left orchiectomy was performed on May 2, 1956 because of a suppurative swelling of the left epididymis A portion of the scrotal skin was also removed because it was markedly adherent to the epididymis Pathological report revealed blastomycosis of the epididymis (figs 1 and 3) The testicle was normal Culture of the epididymis was negative for blastomycosis On May 19, 1956, a transurethral resection biopsy of the prostate gland was performed Pathological report revealed chronic prostatitis There was no evidence of blastomycosis in the biopsied prostatic tissue

The patient was given a second course of stilbamidine therapy in the form of

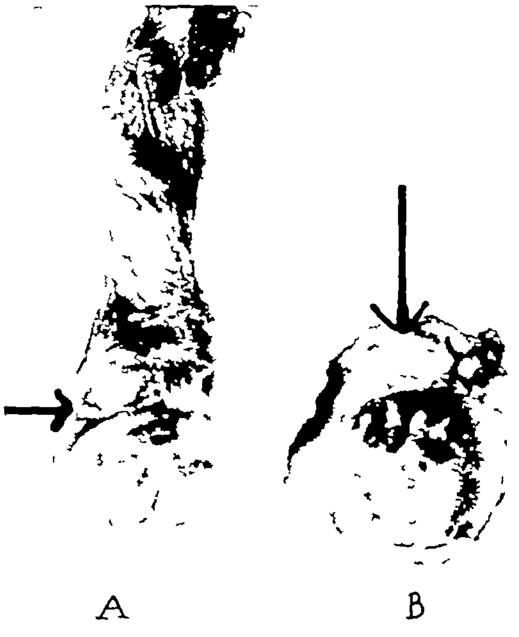

FIG 1 *A*, spermatic cord with sectioned testicle and epididymis showing blastomycotic lesion in epididymis *B* sectioned testicle and epididymis showing blastomycotic lesion in epididymis

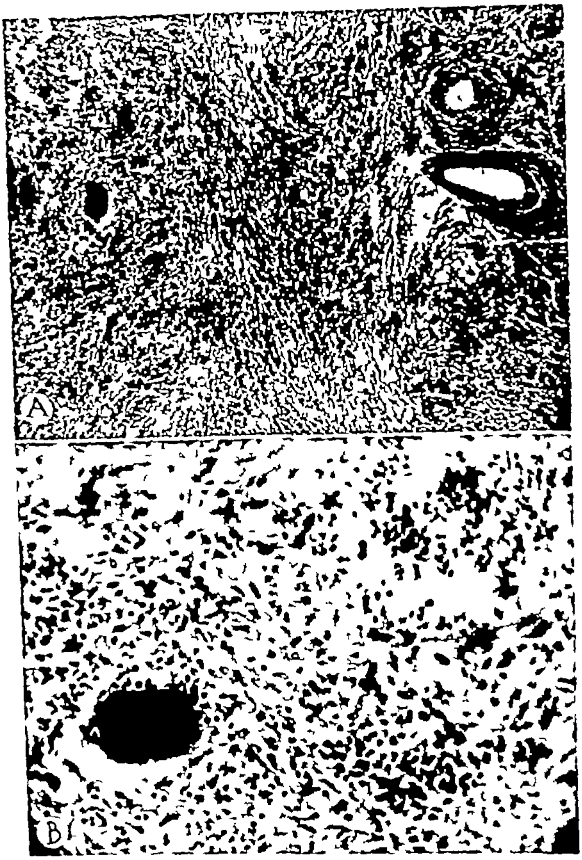

Fig 2 Section through epididymis *A*, low power, shows marked polymorphonuclear leukocyte infiltration and one giant cell *B*, high power, shows polymorphonuclear leukocyte infiltration and giant cell

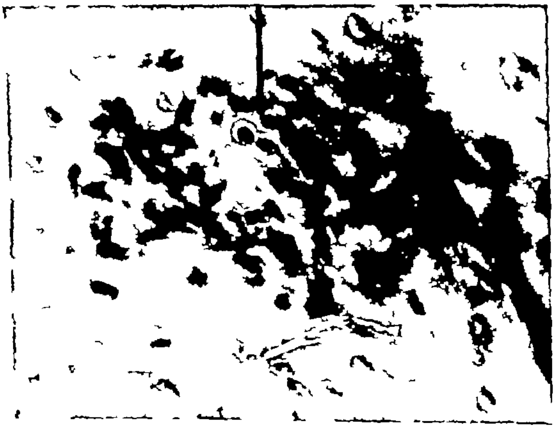

Fig 3 Oil immersion magnification of microscopic section through epididymis shows small round double refractile Blastomyces dermatitidis organism

performed at which time urine specimens were obtained from both kidneys The urine from both kidneys was negative for blastomycosis as well as being sterile on routine culture Bladder urine culture revealed hemolytic Staphylococcus aureus, coagulase negative Blood count, serology, and liver profile were all essentially normal There was a moderate leukocytosis with a normal differential Urinalysis revealed 20 white blood cells per high power field Chest x-ray revealed costophrenic angle pleural thickening, but otherwise was normal Electrocardiogram was normal Skin tests for blastomycosis 1 100 and coccidioidomycosis 1 100 were negative

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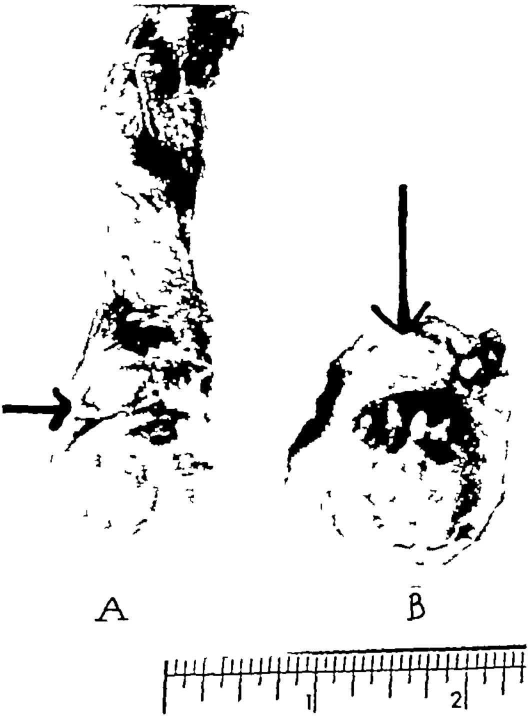

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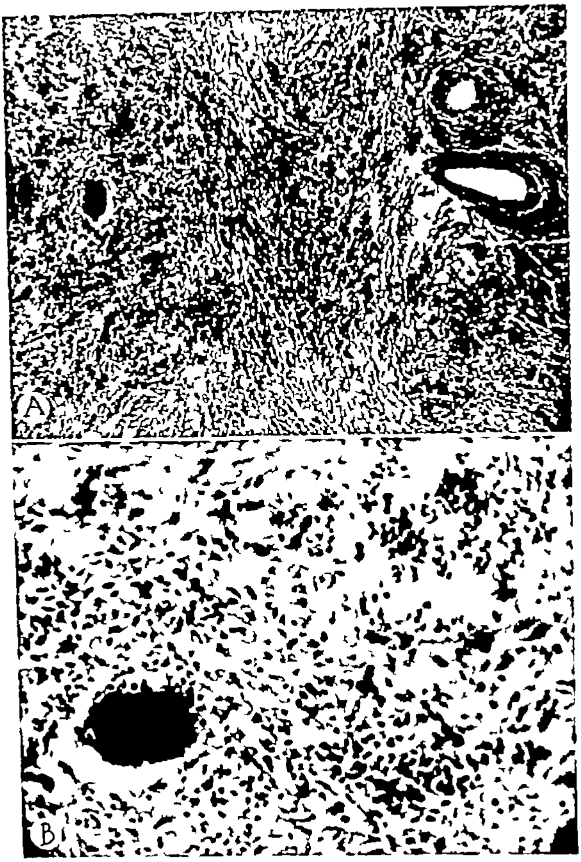

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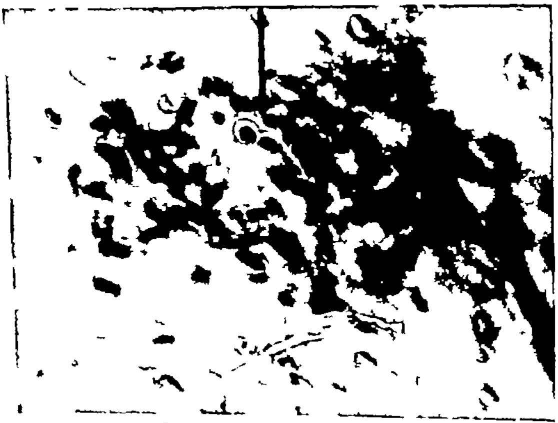

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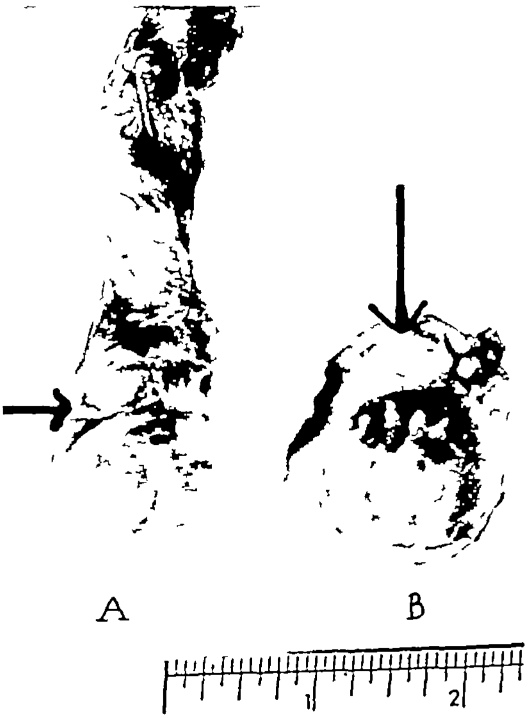

FIG 1 A, spermatic cord with sectioned testicle and epididymis showing blastomycotic lesion in epididymis B, sectioned testicle and epididymis showing blastomycotic lesion in epididymis

Blastomycosis is not contagious Only 4 instances of blastomycosis resulting from inoculation from a known human source are on record (Evans Schwarz and Baum) All of these occurred in physicians or laboratory technicians performing autopsies on cases of systemic blastomycosis

There are no reported cases of blastomycosis resulting from contact with infected urine or prostatic secretions Transmission of blastomycosis during sexual intercourse is theoretically possible but has never been reported

The possibility of an animal reservoir in the transmission of the disease has been considered Blastomycosis has been found in dogs (Foshay and Madden)

INCIDENCE

Blastomycosis is not a rare disease as was once thought With the increase in interest in mycotic infections and the growth of the awareness of the importance of this group of diseases more and more cases of blastomycosis are being reported

The systemic form of the disease occurs in 40 to 50 per cent of all cases of blastomycosis (Friedman and Signorelli Kunkel and associates, Martin and Smith, 1939) The genitourinary system is only involved in the systemic form of the disease Blastomycosis of the genitourinary tract occurs in 20 to 30 per cent of all systemic cases (Friedman and Signorelli, Kunkel and associates, Martin and Smith 1939, Schwarz and Baum, Starrs and Klotz Wade and Bel)

In 1916 Wade and Bel reviewed the literature and found 14 reported cases of genitourinary blastomycosis up to that time In 1939 Martin and Smith collected a total of 25 cases from the literature Since 1939 reviews of cases of blastomycosis from the Mayo Clinic (Kunkel and associates) Milwaukee County General Hospital (Cherniss and Waisbren), Armed Forces Institute of Pathology (Schwarz and Baum) and other sources have brought the total number of reported cases of genitourinary blastomycosis to 76 including the present case report

The lungs, skin subcutaneous tissues, and skeletal system, in this order, are more frequently involved in the systemic form of blastomycosis than the genitourinary tract (Baker Cherniss and Waisbren, Krost, Stober and Moes, Kunkel and associates Martin and Smith, 1939, Schwarz and Baum, Wade and Bel) In the 76 reported cases of genitourinary blastomycosis the kidney was involved in 44 or 57.9 per cent the prostate in 34 or 44.7 per cent, the epididymis in 19 or 25.0 per cent the testicles in 12 or 15.8 per cent the seminal vesicles in 5 or 6.6 per cent the bladder in 4 or 5.2 per cent, and the ureter in 1 or 1.3 per cent

MYCOLOGY

Microscopically Blastomyces dermatitidis is seen in prostatic smears or urine, as double refractile often budding round or oval cells 8 to 20 microns in diameter (fig 3) The addition of a drop of 10 per cent sodium hydroxide or 10 per cent potassium hydroxide facilitates microscopic identification of the organism on wet smear (Conant and associates)

Blastomyces dermatitidis grows well at room temperature on artificial media, but may not culture well in higher temperatures or in the presence of bacteria On blood agar at 37C the fungus develops as a yeast-like organism and has a

2-hydroxystilbamidine At the time of discharge on July 23, 1956, he had no urinary complaints and prostatic smears were negative for blastomycosis

The patient was last seen on November 14, 1956 At this time he had no urinary complaints and prostatic smear was negative for blastomycosis Chest x-ray was essentially normal and there were no cutaneous lesions

DEFINITION

The term blastomycosis refers to North American blastomycosis It is a chronic granulomatous infection caused by Blastomyces dermatitidis The disease was first described by Gilchrist in 1894 and often bears his name North American blastomycosis is to be distinguished from South American blastomycosis which is closely related to coccidiomycosis and European blastomycosis which is actually cryptococcosis

Two clinical types of infection are recognized 1) cutaneous which is limited to the skin, and 2) systemic characterized by dissemination throughout the body

In 1951, Schwarz and Baum proposed that cutaneous blastomycosis is actually a manifestation of systemic disease with the internal focus being a quiescent pulmonary lesion At the present time this concept has not been generally accepted

GEOGRAPHICAL DISTRIBUTION

Blastomycosis is limited to North America In 1948, Starrs and Klotz, in a review of the literature with special emphasis on the incidence in Canada, found over 95 per cent of the reported cases of blastomycosis to be in the United States Blastomycosis is widespread in the United States It is found chiefly in the Southeast, Mississippi Valley, and upper Midwest It is considered endemic in North Carolina (Schwartz and Goldman) At one time it was called "Chicago disease" because a large number of reported cases emanated from Chicago An epidemic of blastomycosis has been reported in the United States (Smith, Harris, Conant and Smith)

AGE, SEX, RACE, SEASONAL INCIDENCE, AND OCCUPATION

Blastomycosis occurs most commonly in the 20 to 50 age group (Friedman and Signorelli, Kunkel and associates, Martin and Smith, 1939) However, cases have been reported in a 6 month-old-infant (Rosenthal) and an 84-year-old man (Sutliff, Kyle and Hobson) The disease is 7 to 15 times more common in men than women (Friedman and Signorelli, Kunkel and associates, Martin and Smith, 1939) There is only one reported case of urinary blastomycosis in the female (Baker) There is no racial predilection and no particular seasonal incidence The majority of cases occur in people working outdoors doing hard manual labor, but there is no one occupation in which the disease is predominant (Friedman and Signorelli, Kunkel and associates, Martin and Smith, 1939)

MODE OF TRANSMISSION

The mode of transmission is unknown However, it is believed the organism enters the body by inhalation through the lungs or through a cutaneous abrasion (Conant and associates) tive therapy for this disease, although administration of iodides in conjunction with vaccine desensitization and x-ray therapy had been reported to have been successfully used in the treatment of some cases (Cummins, Bairstow and Baker)

2-Hydroxystilbamidine, the drug of choice in the treatment of genitourinary blastomycosis, has replaced stilbamidine because it is more stable and less toxic In addition, 2-hydroxystilbamidine does not cause trigeminal neuralgia which is the most distressing toxic effect of stilbamidine However, even with 2-hydroxystilbamidine, immediate toxic reactions such as a fall in blood pressure, sweating, breathlessness, dizziness, nausea, epigastric discomfort, and vomiting occur The drug is contraindicated in the presence of renal and hepatic disease Fatty metamorphosis of the liver and degeneration of the renal convoluted tubules have been reported 2-Hydroxystilbamidine should be administered only in a hospital where the patient can be followed with hepatic and renal function studies, serial x-ray examinations, urinalyses, blood counts, and neurological examinations (Snapper and McVay, Jr)

2-Hydroxystilbamidine is given intravenously by slow drip The dosage varies from case to case, but is usually 5 to 15 grams (Snapper and McVay, Jr) Relapses after treatment with stilbamidine and its analogues have been reported (Sivak and Lich, Jr)

In cases of blastomycosis of the epididymis or testicle surgical excision is indicated There are two reported cases in which prostatectomy was performed for blastomycosis of the prostate (Lewis, Carroll and Stryker, Moore and Halpern) The end result in one of these cases was good (Lewis, Carroll and Stryker) The second patient died shortly after prostatectomy from widespread blastomycosis (Moore and Halpern) There are no reports of nephrectomy for blastomycosis of the kidney

Gentle prostatic massage will help evacuate abscesses in the prostate and expedite healing However, vigorous prostatic massage may disseminate the blastomycotic infection

PROGNOSIS

Prior to the use of stilbamidine and its analogues the prognosis in systemic blastomycosis was very grave Most reviews of the literature revealed that the mortality rate was over 90 per cent in systemic blastomycosis (Cherniss and Waisbren, Martin and Smith, 1939, Schwarz and Baum, Wade and Bel)

The prognosis at the present time is much brighter Stilbamidine and its analogues have a favorable and curative effect in many cases, but relapses have been reported A final and accurate evaluation of the prognosis in cases of genitourinary blastomycosis is still pending

SUMMARY

A case of genitourinary blastomycosis involving the prostate and left epididymis has been presented Initial treatment consisted of stilbamidine followed by a relapse four years later Treatment, following the relapse, consisted of left orchiectomy and a course of 2-hydroxystilbamidine therapy At the present time there is no evidence of recurrence of the blastomycotic infection waxy colony On Sabouraud's medium at room temperature the fungus grows as a mold and appears as a white, cottony growth (Conant and associates)

PATHOGENESIS

Blastomycosis is never primary in the genitourinary tract The organism, in most cases, reaches the genitourinary organs from a pulmonary focus by hematogenous spread Lymphogenous dissemination and spread by direct extension also occur The dissemination of the organism in cases of systemic blastomycosis is similar to that seen in miliary tuberculosis (Schwarz and Baum)

PATHOLOGY

Blastomycotic lesions in cases of systemic blastomycosis are similar in all organs affected The lesions resemble tubercles grossly, but microscopically may be either a collection of blastomyces with a small surrounding area of necrosis, a tuberclelike lesion with central necrosis, epithelioid and giant cells (fig 2), or an abscess rich in polymorphonuclear leukocytes In any of these the lesion is identified by the presence of the organism (Conant and associates)

SYMPTOMS

Genitourinary symptomatology is the main complaint in 2 per cent of all cases of systemic blastomycosis (Cherniss and Waisbren, Kunkel and associates, Martin and Smith, 1939, Schwarz and Baum, Wade and Bel) The most common symptom in genitourinary blastomycosis is dysuria ranging from mild urinary complaints to complete urinary retention Epididymitis is the next most frequently encountered complaint in cases of genitourinary blastomycosis Perineal and suprapubic discomfort are common symptoms Hematuria and hemospermia also occur

LABORATORY FINDINGS

Moderate leukocytosis, elevated sedimentation rate, and anemia are found in most cases of systemic blastomycosis Skin tests and complement fixation tests for blastomycosis are available, but are not reliable because they are only accurate in approximately 50 per cent of the cases (Conant and associates)

DIAGNOSIS

The only absolute diagnostic proof of the disease is by culture However, demonstration of double refractile, often budding, round or oval cells, 8 to 20 microns in diameter in prostatic smears or urine is acceptable proof of the presence of blastomycosis Animal inoculation has also been used with poor results The mouse is the most susceptible animal As previously mentioned, skin tests and complement fixation tests are available, but are not reliable (Conant and associates, Martin and Smith, 1939)

TREATMENT

Prior to the introduction of stilbamidine in the treatment of blastomycosis by Schoenbach and co-workers (1951 and 1952), there had been no generally effec-

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Addendum

Since this paper was submitted for publication another case of genitourinary blastomycosis involving the left epididymis has been seen at Hines Veterans Administration Hospital This brings the total number of reported cases of genitourinary blastomycosis to 77

Blastomycosis is limited to North America Over 95 per cent of the reported cases were in the United States The disease is widespread in the United States

Blastomycosis occurs most commonly in the 20 to 50-year age group The disease is much more common in men than women

The mode of transmission is unknown Blastomycosis is not contagious

Genitourinary blastomycosis only occurs in the systemic form of the disease It occurs in 20 to 30 per cent of all systemic cases There are 76 reported cases of genitourinary blastomycosis in the literature

In the 76 reported cases of genitourinary blastomycosis the kidney was involved in 44 or 57 9 per cent, the prostate in 34 or 44 7 per cent, the epididymis in 19 or 25 0 per cent, the testicles in 12 or 15 8 per cent, the seminal vesicles in 5 or 6 6 per cent, the bladder in 4 or 5 2 per cent, and the ureter in 1 or 1 3 per cent

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Genitourinary symptomatology is the main complaint in 2 per cent of all systemic cases of blastomycosis Dysuria and epididymitis are the most common complaints in cases of genitourinary blastomycosis

The only absolute diagnostic proof of the disease is by culture However, demonstration of the organism in prostatic smears or urine is acceptable proof of the presence of blastomycosis

The drug of choice in the treatment of genitourinary blastomycosis is 2-hydroxystilbamidine However, this drug has certain toxic side effects which are undesirable Surgical excision is indicated in blastomycotic involvement of the epididymis or testicle

Prior to the introduction of stilbamidine the prognosis in systemic blastomycosis was grave At the present time the prognosis is brighter, but relapses have been reported following therapy with stilbamidine and its analogues A final and accurate evaluation of the prognosis in cases of genitourinary blastomycosis is still pending

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L-4 area of the spine and 1500 r in air to the right groin Some temporary benefit followed this treatment, but pain soon recurred and became intractable He returned to the New England Deaconess Hospital on February 11, 1957, less than one year after orchiectomy At this time an x-ray film of the pelvis revealed diffuse osteoblastic metastases typical of prostatic carcinoma The serum acid phosphatase determination was 9 9 Bodansky units and the hemoglobin 11 2 gm per cent The prostate gland was large, hard and irregular, apparently without definite change since the previous examination Bilateral cervical chordotomy was advised and carried out in stages on February 15 and February 21, 1957 Prompt relief of pain followed In the hope that there might be some control of of this rapidly spreading process, stilphostrol was prescribed, 100 mg, intramuscularly, daily One month later the serum acid phosphatase was 1 79 Bodansky units and the alkaline phosphatase 13 3 Bodansky units He was discharged home on March 31, 1957 to continue taking stilphostrol by mouth, 100 mg per day

Here, then, we have a patient with apparently typical adenocarcinoma of the prostate which never showed the usual response to hormonal treatment and was associated with uncontrollable pain, severe enough to require chordotomy, 19 months after the onset of symptoms

Case 2 New England Deaconess Hospital No 65884 A business executive, aged 70, was first seen in consultation on September 13, 1955 He had had increased frequency of urination for 1 year and a few months previously, in another hospital, had had a suprapubic operation for the removal of bladder stones The surgeon decided to remove the prostate at the same time because it was quite large, but he found the gland to be malignant and complete enucleation was impossible When we first saw the patient, his wound was well healed and he had no symptoms He had been taking stilbestrol for about 3 months The general condition was excellent Cystoscopic examination found the bladder to be negative, no tumor was to be seen and no significant prostatic obstruction Rectal examination found a firm plaque in the region of the prostate, too extensive for surgical removal The serum acid phosphatase was normal No metastases were seen in x-ray films of the chest, lumbar spine and pelvis The original slides were reviewed by Dr Warren who made the diagnosis of "undifferentiated carcinoma, more malignant than usual carcinoma of prostatic origin " A bilateral orchiectomy was performed and the patient left the hospital October 4, 1955 Later as an outpatient, he received 28 x-ray treatments with 2 million volts and rotation of the pelvis with a port measuring 10 cm in diameter The calculated dose in the bladder was 4412r Estrogen therapy was continued

The patient returned to the hospital in January 1956, because of pyelonephritis and renal colic due to a small uric acid stone There were no x-ray signs of metastases The serum acid phosphatase was normal He was leading an active life but, in the succeeding months, there was some evidence on office examination that the hard mass in the region of the prostate was becoming more extensive He re-entered the hospital in October 1956 with acute urinary retention and a transurethral resection was required There were no signs of metastases and the serum acid phosphatase determination was 6 Bodansky units At the time of the

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HORMONE-INDEPENDENT CANCER OF THE PROSTATE

ROGER C. GRAVES, ROBERT E. DESAUTELS AND SHIELDS WARREN

It is common knowledge that certain cases of prostatic cancer do not respond to hormone therapy in the usual way. Woodard and Dean in 1947, for example, found approximately ten per cent of such cases in their series. While we believe the average incidence to be somewhat less than this, these refractory tumors present such difficult problems when they do occur that further study of their nature and behavior seems of interest. The following three cases observed during the past two years form the basis of the present discussion.

CASE REPORTS

Case 1. N. E. Deaconess Hospital No. 70322. A 71-year-old man was admitted to the New England Deaconess Hospital for the first time on February 26, 1956 because of pain in his low back, right groin and right hip which began in July 1955 and became progressively severe over the ensuing months. In September 1955 a transurethral resection of the prostate had been performed elsewhere because of difficulty with voiding, hesitance and dysuria. A histologic diagnosis of adenocarcinoma of the prostate gland was made and therapy with stilbestrol, 1 mg. q.d. was instituted. Despite hormonal therapy the pain continued to become progressively worse and the patient lost 30 pounds in weight.

On examination he was found to be in a generally good physical state. Some enlargement of the liver was present to two finger breadths below the costal margin. Tenderness was noted in the right groin and over the right ascending pubic ramus. Rectal examination revealed an extensive, hard, irregular area in the region of the prostate gland consistent with carcinoma. Routine laboratory studies were within normal limits save for 20–25 white blood cells in the urine. Acid phosphatase determination was 0.18 Bodansky units. The lung fields were clear. X-rays revealed compression of vertebrae D-6 and L-1 with osteolytic changes in the bone possibly related to metastatic carcinoma of the prostate but not typical in appearance. X-ray films of the lumbar spine and pelvis were otherwise negative. A total of 1500 r of x-ray therapy was given to the involved areas of the spine from March 1 to March 15, 1956 because of the equivocal appearance of the x-rays. Bilateral orchiectomy was performed on March 7. The patient took stilbestrol, 10 mg. a day, during the first ten days of his hospital stay and then 1 mg. a day thereafter. At the time of his discharge, March 25, 1956, he was somewhat better but still complained of discomfort in the region of the right groin. Estrogen therapy was continued.

The patient continued to have pain at home but showed some improvement for a few months, though the mass in the prostate remained large and quite firm. When he was seen in October 1956, pain had again become a severe problem. He took meticorten, 10 mg. three times a day, for a short period without relief. X-ray therapy was again employed, a dose of 2100 r in air being given to the D-11,

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The lung fields were clear by x-ray. Films of the pelvis and left hip showed only soft tissue calcification at the margin of the greater trochanter of the left femur. Intravenous pyelograms were normal except for some elevation of the floor of the bladder consistent with enlargement of the prostate.

When first seen in urological consultation on December 6, 1955, the patient had no urinary symptoms. The prostate was of normal size on rectal examination, it was firm and uneven with ill-defined upper limits. The changes were thought to be suggestive of prostatitis rather than tumor.

Cystoscopy found no residual urine. There was edema of the distal trigone. Around the outlet of the bladder in the internal sphincter margin and, to some extent, in the immediately adjacent bladder mucosa, were multiple hemorrhagic areas which might well have been the source of bleeding and which now would suggest an inflammatory process in the underlying prostate. In the bladder, some of these areas were slightly suggestive of interstitial cystitis. There were shreds of adherent fibrin and one or two small, white nodules like pustules. There was no significant obstruction to be seen at the bladder neck or within the prostatic urethra. Rectal examination with the patient relaxed under spinal anesthesia found questionable thickening in the seminal vesical region with no suggestion of tumor. The prostate was slightly enlarged and uneven in consistency and in some areas a little firm, but the gland appeared to be confined within its capsule and it was thought that the changes were probably due to prostatitis. A program of antiseptic medication was ordered, but it was noted that the prostate should be kept under observation by means of occasional office visits.

The clinical response to treatment was not convincing. The patient still reported slight burning on urination and some dribbling after voiding. The cystoscopic examination was repeated four days later. The instrument passed very easily through a soft and flexible bladder neck. The signs of inflammation were less marked. There was still no prostatic obstruction to be seen and no tumor, but, in the outlet of the bladder in the right lower quadrant, there was a slight, pale elevation which was chosen as a site for biopsy. One segment of tissue was removed with the resectoscope. The pathological report was as follows: "Portions of prostate and urethra. One fragment of prostate is free from tumor. The remaining fragments, most of which include urethra, are involved by carcinoma which grows in sheets and nests, with anaplastic cells and mitotic figures, the cells being rather plump with pink-staining cytoplasm and resembling squamous or transitional type cells. The tumor is growing in endothelial lined spaces. There is an accompanying nonspecific chronic inflammatory reaction. This type of tumor could be primary in the urethra or in the urinary bladder." After consultation with Dr. Warren, the diagnosis was made of carcinoma simplex of the prostate with epidermoid characteristics as shown in figure 1.

Stilbestrol, 10 mg. intramuscularly, was prescribed daily, and the patient was discharged from the hospital December 20, 1955, to continue on estrogen therapy and to permit the healing of his bladder neck before surgery. He returned on January 6, 1956. Dysuria and dribbling were less. The slight discomfort in the left sacroiliac region, which had been thought to be unrelated to the prostate, resection, no actual tumor could be seen but quite marked obstruction at the bladder neck was present The tissue removed showed carcinoma, unclassified

Retention soon recurred and transurethral resection was repeated on December 5, 1956 The tissue removed at this time was again described as undifferentiated carcinoma Thrombophlebitis of the right leg and hematuria on dicumarol therapy brought the patient back to the hospital three weeks later, but nothing more than brief catheter drainage was required The serum acid phosphatase determination was normal He became progressively weaker and he complained of persistent discomfort on urination A large mass was present in the region of the prostate and bladder Thrombophlebitis developed in the left leg and left arm X-ray film of the chest and pelvis on March 4, 1957 showed no evidence of metastatic tumor Estrogen therapy was continued together with meticorten The serum acid phosphatase on April 1, 1956 was 3 0 Bodansky units and the serum alkaline phosphatase was 5 2 Bodansky units On April 12, 1957, less than two years from the time of prostatectomy, a permanent suprapubic cystotomy became necessary Exploration through the open bladder found practically complete obstruction at the bladder neck with extension of the mass in this region upwards on the right side, beginning to encroach upon the bladder cavity and probably occluding the right ureter

This patient had a highly undifferentiated carcinoma whose site of origin might well be in doubt, if the diagnosis depended upon examination of the histologic sections alone However, the clinical behavior of the neoplasm associated with a late elevation of the serum acid phosphatase allows it to be classified as tumor derived from prostate and not from bladder or urethra The metastases that he must surely have are lymphatic, since they have not appeared in the usual areas The slow rise in serum acid phosphatase, despite a large amount of gross tumor, is probably in keeping with the poor differentiation of the lesion, since it is known that immature prostatic tissue produces only very small amounts of acid phosphatase

Case 3 Carney Hospital No 56-458 This case will be reported in greater detail because it illustrates so well the problem under discussion

A clergyman aged 53, unmarried, was admitted to the Carney Hospital, November 29, 1955 He complained of burning discomfort on urination with increased frequency, and tenderness in the region of the left hip He had noted these bladder symptoms intermittently and with occasional diminution of the urinary stream during the previous few years Two years before, he had seen a few spots of blood on his underwear and this had recurred once recently Seven weeks before admission, he fell and injured his back and tenderness persisted in the left hip There was no familial history of cancer

Physical examination found a well developed and well nourished man of 53 whose vital signs were normal The initial study was negative except for tenderness on deep palpation in the left hip region The urine showed 20-25 red blood cells and 4-6 white blood cells in the sediment The reports of blood counts and blood chemistry were normal The serum acid phosphatase was 1 2 King units The alkaline phosphatase was 4 6 Bodansky units

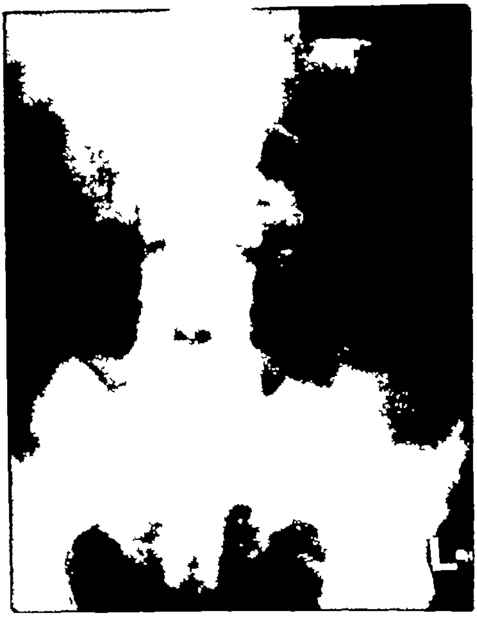

FIG 2 Case 3 X-ray of lumbar spine and pelvis shows diffuse osteoblastic metastases

ketosteroids were 4 9 mg /24° The serum acid phosphatase determination was 4 Bodansky units and the alkaline phosphatase was 22 7 Bodansky units X-ray examination found the lungs to be clear but there were osteoblastic metastases in all of the ribs and in the clavicles and in all of the bones of the spine and the pelvis (fig 2) There was definite increase in the extent of disease since the previous films of only four weeks earlier Six x-ray treatments with a total airdose of 1500r were given to a single port directed into the left side of the pelvis with 2 million volt equipment The patient was discharged home February 18, 1956, at which time the acid phosphatase determination was 2 Bodansky units and the alkaline phosphatase 17 1 Bodansky units Final diagnosis Epidermoid carcinoma of prostate with metastases

Pain persisted requiring opiates and in spite of continued estrogen and meticorten therapy, he died in July 1956, within ten months of the beginning of his illness

Insufficient data exist with regard to the epidermoid tumors, because of their rarity, as to whether or not they are uniformly resistant to hormonal therapy In the case at hand there appears to be an association between resistance to hormonal therapy and the epidermoid differentiation

In our experience epidermoid carcinoma of the prostate is a rare lesion While a number of cases have been reported in the literature, most of these fail to give data as to the hormonal response of the tumors However, two of the three cases reported by J C Sieracki in 1955 were noted to be poorly responsive to hormonal therapy

The Mayo Clinic experience seems to be along the same lines Thompson,

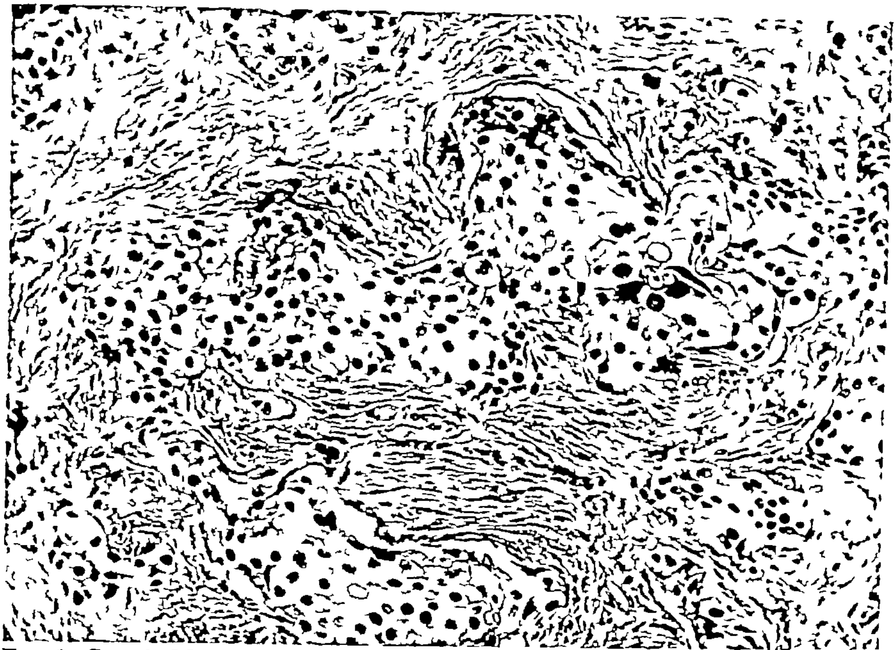

FIG 1 Case 3 Microscopic section of prostate shows carcinoma simplex with epidermoid characteristics ×260

was better The gland was still small but now smooth and less firm The serum acid phosphatase was 1 3 King units The hemoglobin had dropped from an initial 15 gm to 13 5 gm The urine showed 30–35 red blood cells No metastases were seen in the x-ray films of the lumbosacral region Total perineal prostatectomy was advised and was planned for two weeks later, after continued estrogen therapy

The patient returned to the hospital January 17, 1956 He had seen blood in the urine on one recent occasion In spite of the usual dosage of stilbestrol, his back pain had become progressively worse X-rays of the pelvic bones, which had been thought to be negative less than two months before, now showed definite osteoplastic metastases in the ilium on each side, and in the upper femur on the left side, and in the first lumbar vertebra These were quite consistent in their appearance with rapidly spreading carcinoma of the prostate The rectal examination still found a small prostate well within normal limits of size and without definite changes that would indicate the presence of tumor The plan for total perineal prostatectomy was abandoned and bilateral orchiectomy was performed on January 20, 1956 At this time the serum acid phosphatase was 2 9 King units One week later, with his backache still unrelieved, the patient was transferred to the New England Deaconess Hospital for x-ray therapy

At the Deaconess, Dr J Hartwell Harrison saw the patient in consultation, estrogens were continued and meticorten was added to the program Prior to administration of meticorten, control values of 24-hour urinary 17-hydroxycorticoids and 17-ketosteroids were 4 4 mg and 18 2 mg respectively One week after treatment was started the 17-hydroxycorticoids were 6 1 mg 24° and the 17-

The production of acid phosphatase by the prostate gland is a secondary sex characteristic according to Huggins Immature prostatic tissue contains very little acid phosphatase and it is not until after puberty that the normal adult tissue level is attained, representing a several hundred-fold increase in concentration The production of acid phosphatase is therefore an attribute of adult tissue and may be used in comparing various prostatic cancers The level of serum acid phosphatase appears to correlate with the degree of tumor differentiation in that patients with undifferentiated or immature lesions tend to have a low value Serum and tissue phosphatase measurements are not necessarily proportional to one another in a given patient Normal adult prostatic tissue has about twenty times as much acid phosphatase per gram as the average tumor (Huggins 1946–47) and yet very little of this substance is detectable in the blood Though we do not have much direct evidence to support the idea it seems that the immature types of tumor, as well as the immature normal prostate gland, produce very small amounts of acid phosphatase (Sullivan Gutman and Gutman 1942)

The response to estrogen and orchiectomy following obvious metastases is not usually as definite or as prolonged as it is in more localized lesions (Nesbit and Baum, 1950) The fact that a metastasis can grow in a new area away from the parent tumor suggests a basic change in the tumor cells toward more independent behavior and greater growth potentiality

As yet no clear physiological or biochemical difference has been demonstrated between the normal male and the male with prostatic carcinoma Whether the endocrine changes that take place in man during the process of aging have any bearing on the production of prostate cancer cannot be discerned At the time of life when prostatic carcinoma is most common the endogenous supply of androgen has already become greatly reduced (Hamburger, Halvorsen and Pedersen, 1945) It is obvious that a more concentrated study of the individual patient and his tumor is needed to bring further light on these problems

It is important to recognize the fact that certain patients do not respond to androgen removal or suppression and that demonstration of initial hormone dependence does not insure a continuing beneficial response Since the result of hormonal treatment cannot be predicted with assurance surgical removal of prostatic tumors should be accomplished whenever possible

SUMMARY

A small group of prostatic tumors representing the minority which show no initial response to hormonal therapy is reported

These neoplasms are often undifferentiated in type

As yet no definite pattern of hormonal change has been seen in patients with carcinoma of the prostate gland and yet more careful scrutiny of the individual patient may be extremely revealing

Finally it is strongly urged that hormonal therapy should not be substituted for total prostatectomy in the treatment of carcinoma of the prostate when conditions are favorable for surgical extirpation of the disease

12 Bay State Road Boston 15, Mass

Albers and Broders (1953) believe hormonal therapy to be ineffective in tumors of this type

There has been considerable speculation as to the type cell from which these epidermoid carcinomas arise In general, it is felt that the tumors do not arise from metaplastic epithelium but rather arise from undifferentiated cells residual from the primitive embryonic outpocketings of the urethral mucosa that form the prostate in the adult We agree with the general line of reasoning proposed by R A Willis (1950) in his discussion of the origin of this form of prostatic carcinoma These epidermoid carcinomas are frequently very poorly differentiated and anaplastic in type The squamous metaplasia seen in the prostatic ducts and acini that follows estrogenic therapy is of a different type, being noninvasive and rather uniform

DISCUSSION

It is indeed fortunate, and perhaps somewhat surprising (in comparison with other tumors) that so many prostatic neoplasms are dependent upon androgen for continued growth Maturity of cell structure in general appears to be essential for the normal response of a glandular structure to its trophic hormone as, for example, in the case of adrenal tumors Most prostatic tumors appear to have some of the characteristics of adult tissue and this probably accounts for their commonly observed hormone dependence In spite of this observation, it has not been possible in the past to establish a definite correlation between histologic appearance of prostatic tumor and response to hormonal therapy (Foot, Humphreys and Coats, 1950) However, as far as we can determine, the very undifferentiated tumors, especially those of the epidermoid type, do not respond to estrogen therapy and orchiectomy

The group of tumors reported here represents a spectrum of tumor growth proceeding from partial differentiation to complete immaturity of cell type Each neoplasm in this small series, though different in histology, shares a general unresponsiveness to changes in the hormonal environment, although in the first case, lowering of the serum acid phosphatase after use of stilphostrol may indicate some biochemical response In the third case presented, it is to be noted that a normal total urinary 17-ketosteroid value was present after orchiectomy and that during meticorten administration the value was markedly reduced, suggesting a suppression of adrenal androgen supply Obviously in this case, suppression of adrenal activity was of no aid in relieving the patient

The in vitro observation of Lemon, Wotiz and Robitscher (1953) that, in general, slices of prostatic carcinoma destroy greater amounts of testosterone than do normal prostatic tissue slices, suggests a greater androgen requirement of tumor tissue and implies a greater sensitivity to withdrawal of male hormone Huggins has shown that androgen can hasten the progression of prostatic carcinoma The increased ability of tumor cells to metabolize testosterone may be in part a manifestation of increased metabolic activity rather than increased biologic need One very immature tumor reported in Lemon's series showed no measurable destruction of testosterone The third case in our series, representing an epidermoid lesion, may be of a similar type

The production of acid phosphatase by the prostate gland is a secondary sex characteristic according to Huggins Immature prostatic tissue contains very little acid phosphatase and it is not until after puberty that the normal adult tissue level is attained, representing a several hundred-fold increase in concentration The production of acid phosphatase is therefore an attribute of adult tissue and may be used in comparing various prostatic cancers The level of serum acid phosphatase appears to correlate with the degree of tumor differentiation in that patients with undifferentiated or immature lesions tend to have a low value Serum and tissue phosphatase measurements are not necessarily proportional to one another in a given patient Normal adult prostatic tissue has about twenty times as much acid phosphatase per gram as the average tumor (Huggins, 1946–47) and yet very little of this substance is detectable in the blood Though we do not have much direct evidence to support the idea, it seems that the immature types of tumor, as well as the immature normal prostate gland, produce very small amounts of acid phosphatase (Sullivan, Gutman and Gutman, 1942)

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As yet no clear physiological or biochemical difference has been demonstrated between the normal male and the male with prostatic carcinoma Whether the endocrine changes that take place in man during the process of aging have any bearing on the production of prostate cancer cannot be discerned At the time of life when prostatic carcinoma is most common the endogenous supply of androgen has already become greatly reduced (Hamburger, Halvorsen and Pedersen, 1945) It is obvious that a more concentrated study of the individual patient and his tumor is needed to bring further light on these problems

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CHANGES IN MICROSCOPIC PATHOLOGY OF PROSTATIC CARCINOMA FOLLOWING ESTROGEN THERAPY AND SURGERY

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The necessity to re-operate for obstructive carcinoma of the prostate has presented itself from time to time The pathologist's report of the tissue then submitted has often shown that a change has taken place some time in the period between the first operation and the onset of symptoms leading to the necessity for another operative procedure Where the tissue at first showed clearly differentiated cells of adenocarcinoma, the pathologist's subsequent report has been undifferentiated carcinoma What is of particular interest, is that it soon became evident that this microscopic change was a landmark in the response of the patient to any type of therapy The loss of hormonal response of the tumor became evident not only by the microscopic changes seen, but also by the clinical results of therapy From then on the patient failed to respond to estrogens, cortisone, or x-ray therapy and lost ground rapidly

The authors here review several cases which demonstrate this change from well differentiated adenocarcinoma to undifferentiated or transitional cell carcinoma of the prostate

CASE REPORTS

Case 1 A W, a 63-year-old white diabetic man, was seen in January 1952 with obstructive prostatic symptoms He had a large amount of residual urine and the prostate was found to be enlarged, hard and fixed Intravenous pyelogram was normal except for the presence of a large prostate The acid phosphatase was found to be normal In February 1952 a transurethral resection of the prostate was done and the frozen sections showed adenocarcinoma Bilateral orchiectomy was done The microscopic diagnosis was adenocarcinoma of the prostate (fig 1, *A*)

The patient made an uneventful recovery He was placed on stilbesterol, 5 mg b i d, and later on dienestrol 10 mg b i d He did quite well until September 1955 when he experienced recurrent symptoms of prostatism with residual urine of six and one-half ounces (residual urine had been down to two ounces) In October 1955 transurethral resection was repeated Microscopic examination of the tissue disclosed transitional cell carcinoma (fig 1, *B*) The patient recovered well from the operative procedure, and was discharged on 1 mg of stilbesterol daily Followup visits revealed residual urine of from zero to one-half ounce On rectal examination the prostate remained very hard and nodular The patient began to have severe leg pains thereafter, and in November 1955 was started on TACE In January 1956, he had the first of many episodes of bleeding

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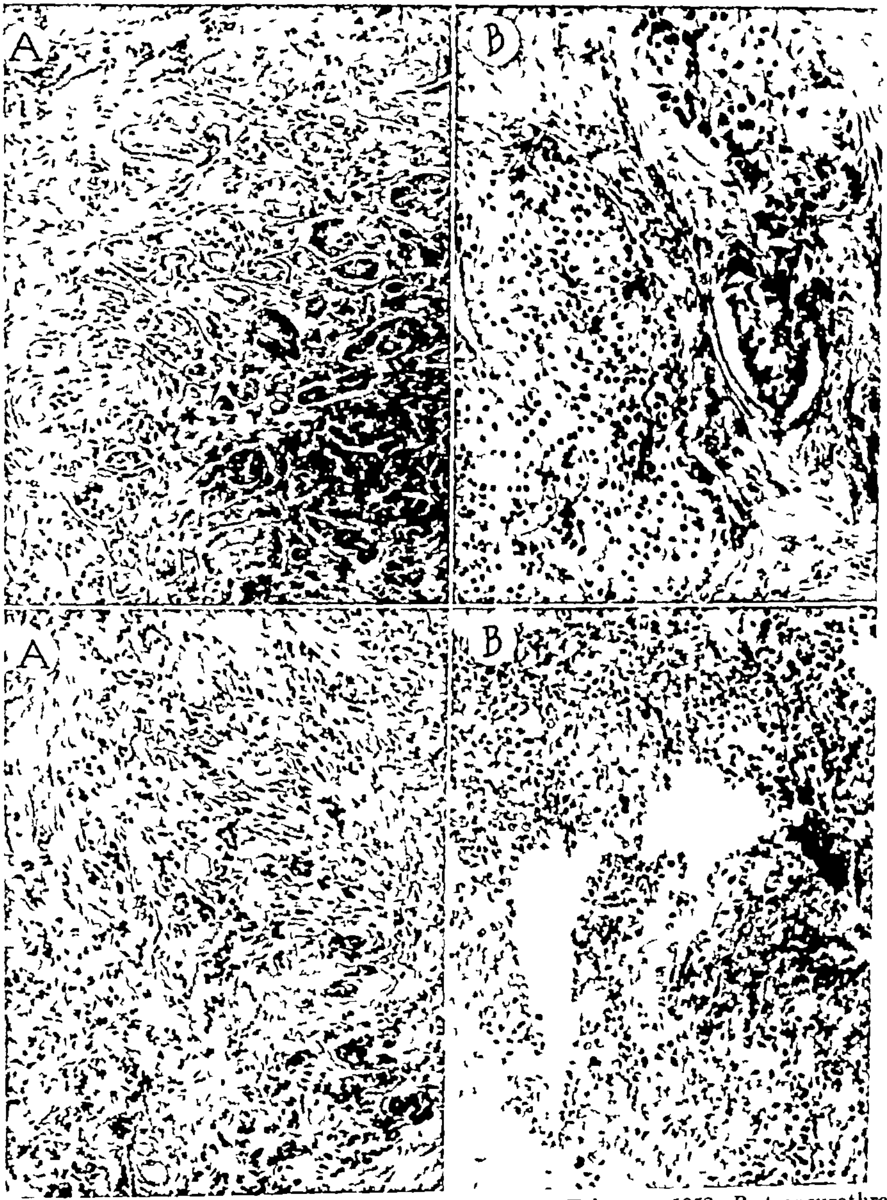

FIG 1 A and B, case 1 A, transurethral resection, February 1952 B, transurethral resection, October 1955
C and D, case 2 C, transurethral resection, August 1947 D transurethral resection, March 1952

from the prostate (five such episodes in January and February 1956) Each episode was treated by irrigations to the bladder through an indwelling Foley catheter On one occasion it was necessary to fulgurate the bleeding areas These episodes of hematuria were usually precipitated by a bowel movement

In January 1956 he was started on cortisone In February 1956, deep x-ray therapy to the region of the prostate was instituted in an attempt to prevent further bleeding He did fairly well for a while, but the following month required fulguration for arterial bleeding from the prostate In April this had to be repeated He continued to have frequent episodes of bleeding thereafter, although he was placed on constant urethral catheter drainage Finally in July 1956 a permanent cystotomy was done The patient's course was progressively downhill thereafter He had many episodes of bleeding, one requiring fulguration He became gradually more cachectic and died on November 13 1956

Case 2 J R , a 67-year-old white man, was first seen in August 1947, with the chief complaint of hematuria and dysuria Urinalysis revealed many erythrocytes Residual urine was two and one-half ounces The prostate was enlarged, irregular and nodular on rectal examination Cystoscopy revealed moderate prostatic enlargement

Later in August 1947, a transurethral resection of the prostate and bilateral orchiectomy were done The pathologist's report was adenocarcinoma of prostate, poorly differentiated in many areas (fig 1, *C*)

The patient did well until June 1951, when symptoms of prostatism recurred By January 1952, he had nocturia five to six times, and a poor urinary stream The residual urine was three ounces Cystoscopy revealed encroachment of the prostatic carcinoma into the bladder inverted V at 12 o'clock and moderate slough within the urethra The patient was started on stilbesterol 5 mg t i d and in March 1952 he underwent a secondary transurethral resection There was marked invasion under the right side of the bladder floor The pathologist's report was undifferentiated carcinoma of the prostate (fig 1, *D*)

By June 1952, the patient began to appear cachectic Two months later ano-

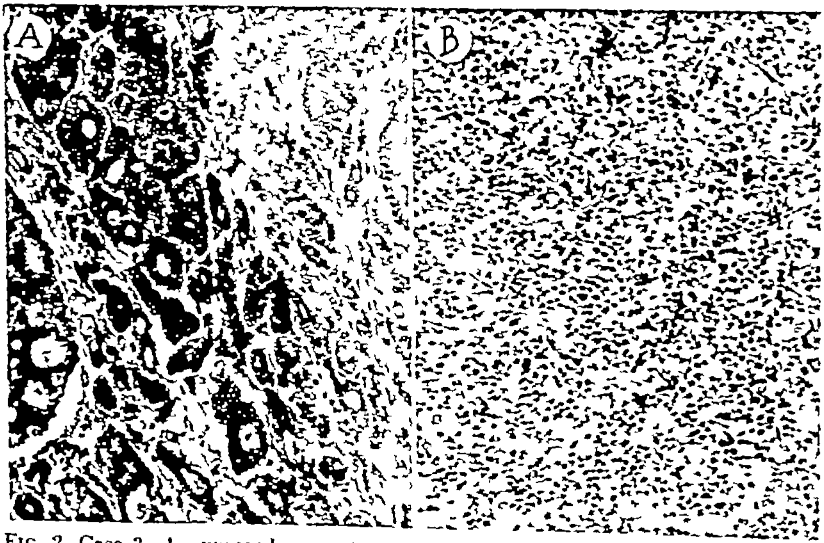

FIG 2 Case 3 *A* suprapubic prostatectomy April 1950 *B* transurethral resection, April 1951

TABLE 1

	Case 1	Case 2	Case 3
First operative procedure	TUR & orchiectomy, Feb 1952	TUR & orchiectomy, Aug 1947	2nd stage suprapubic prostatectomy, April 1950
Pathologist's first diagnosis	Adenocarcinoma	Adenocarcinoma with areas of poor differentiation	Well differentiated adenocarcinoma with areas of perineural involvement
Second operation	TUR, Oct 1955	TUR, March 1952	TUR & orchiectomy, April 1951
Pathologist's second diagnosis	Transitional cell carcinoma	Undifferentiated carcinoma of prostate	Undifferentiated carcinoma of prostate
Estrogen therapy	Feb 1952, stilbesterol, Jan 1955, cortisone, Nov 1955, TACE	Jan 1952, stilbesterol, Mar 1952, premarin, later cortisone	Apr 1950, stilbesterol, 1951, x ray therapy, vallestril
Clinical course	Died Nov 1956, cachexia & repeated episodes of prostatic bleeding (13 months after 2nd TUR), known duration of disease, five years	Died Jan 1953, cachetic (10 months after 2nd TUR), known duration of disease, 5½ years	Died April 1952 (12 months after 2nd TUR), known duration of disease, 2½ years

rexia, vomiting and lethargy developed He was given trials on premarin and cortisone, all to no avail In January 1953, after several weeks in bed, he died

Case 3 M E, a 58-year-old white man, was first seen in April 1950 with the chief complaint of painless hematuria of six weeks' duration Prostatic enlargement was found, and a suprapubic prostatectomy was done Enucleation was difficult The pathologist's report was adenocarcinoma, moderately well differentiated, invading lymphatics (fig 2, *A*) The patient recovered satisfactorily, and was started on stilbesterol, 2 mg three times daily The patient began to have intermittent hematuria and therefore, in March 1951, cystoscopy was done Findings were those of prostatic enlargement intravesically, an inverted V at 12 o'clock, and tortuosity of prostatic urethra In April 1951, x-rays revealed metastases to the ilium, spine and ribs Transurethral resection of the prostate and bilateral orchiectomy were done The pathologist's report was undifferentiated carcinoma of the prostate (fig 2, *B*) The patient lived for one year after operation Large doses of estrogens and x-ray therapy were given to no avail

In attempting to better evaluate these cases by way of similarities and differences, the tabulation may be helpful (table 1)

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[1] Sutton, E B and McDonald, J R Am J Clin Path, **13** 607-615, 1943

DISCUSSION

Sutton and McDonald[1] have done an extensive study of prostatic epithelium, with special reference to squamous metaplasia They state that islands of epithelium resembling squamous epithelium are seen frequently in the depths of the prostate They studied four groups of material routine postmortem examinations, transurethral resections for benign prostatic hyperplasia, prostatic calculi, and abscesses, cases in which the microscopic diagnosis of prostatic infarct was made on transurethral resection, and secondary transurethral resection from one to two weeks after the first resection

They found in the postmortem specimens, that the epithelial lining of the prostatic ducts varied from a single layer of columnar epithelium to stratified squamous epithelium in more superficial parts In some cases, stratified squamous epithelium lined ducts for a depth of two to three rows On specimens from transurethral resection they found squamous metaplasia in 15 9 per cent These changes were usually confined to a small portion of one lobe, and were never generalized They were seen usually in one of the lateral lobes, situated far from the urethral epithelium Histologically, they were suggestive of squamous epithelium These changes were seen in cases of benign prostatic hyperplasia No metaplastic changes were seen in the twelve cases of multiple calculi or in eight cases of chronic abscess studied Metaplasia was seen in 36 6 per cent of cases of prostatic infarct The areas of metaplasia were seen only in and about the infarcted areas On secondary resections, squamous metaplasia was found in 51 9 per cent It could be seen beneath the necrotic edge of cut surface of the prostate It was felt that it might help in part of epithelialization of the prostatic bed Sutton and McDonald express the opinion that as a result of the stimulation from areas of necrotic tissue in prostatic infarct and after transurethral resection of prostate, marked regeneration is occurring and there is, therefore, increased likelihood of metaplasia

Broders[2] has noted that in many organs, as a response to a stimulus (as in wound healing), a "non-malignant" hyperplasia often results The cells involved in this hyperplasia may even penetrate beyond the normal juncture between epithelium and connective tissue, although no neoplastic cells are present

Parkes and Zuckerman[3] have shown that estrogens can cause increased stratification of epithelium and foci of squamous metaplasia in the prostatic utricle It has been shown by Heckel and Kretschmer[4] that estrogen therapy can cause the cells of a prostatic carcinoma to undergo hydropic degeneration and vacuolation

Nicol and associates[5] showed suggestive evidence that estrogen administration, especially when combined with orchiectomy, assists in the mobilization of reticulo-endothelial cells, which can later become fibroblasts, according to Maximow and Bloom [6] In guinea pigs so treated they saw increased prostatic fibrosis

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[2] Broders, A C J A M A 99 1670–1674 1932

[3] Parkes A S and Zuckerman S Lancet 1 925–928, 1935

[4] Heckel N J and Kretschmer, H L J A M A 119 1087, 1942

[5] Nicol T, Helmy I D and Abou Zikry A Brit J Surg, 40 166–172 1952

[6] Maximow, A A and Bloom William Textbook of Histology, 5th ed Philadelphia W B Saunders Co 1948 p 114

Thus, fibrosis of the neoplastic prostate resulting from this therapy may be due to the accumulation of reticulo-endothelial cells in that organ

There is, therefore, good background evidence for explanation of microscopic changes which one might expect to find in the cases previously described As noted previously, these were not the changes found Instead, in these cases, either a more poorly differentiated neoplasm was found, or one in which the microscopic pathology had dramatically changed

In the three cases reported here, each patient was dead within 13 months of the secondary transurethral resection Unfortunately, postmortem examination could not be obtained for further microscopic studies of the prostate

It is at present unknown whether the changes in microscopic pathology and biological activity (loss of hormonal relationship) were part of the natural history of the neoplasms discussed One can only speculate about the possibility of their having been caused partially or entirely by the operative procedures done, or by the administration of estrogens We wish only to raise these questions for further consideration and study, and emphasize the point that the change in the microscopic pathology seemed to be a landmark in the clinical response of the patient to estrogen or cortisone therapy

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CALCIUM STUDIES IN TEN CASES OF OSTEOBLASTIC PROSTATIC METASTASIS

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Urine and serum calcium studies often provide a practical, accurate indication of the extent of breast carcinoma in patients in whom metastasis to bone has taken place The quantity and rate of osteolysis in the metastatic lesions is directly correlated with urinary calcium excretion in most of these patients

Although in breast carcinoma metastasis is usually osteolytic, it is predominantly osteoblastic in 8 per cent of the cases Even in patients with roentgenographic evidence of primarily osteoblastic metastasis, serum alkaline phosphatase has been inversely related to serum calcium levels [1] Increasing serum alkaline phosphatase activity was associated with decreasing serum calcium levels in 94 per cent of 32 cases, and decreasing serum alkaline phosphatase activity, with increasing serum calcium levels, in 91 per cent of 33 cases These findings suggested the possibility of relating chemical changes in urine and blood with osteoblastic bone involvement

Precise measurement of calcium balance in patients is so complicated that it is practical only in special studies, but urinary excretion of calcium is readily studied Excretion of excessive calcium takes place earlier and is a more sensitive indicator of bone destruction than is an increase in serum calcium Hypercalcemia does not appear until urinary calcium excretion exceeds 500 mg per day when the patient is on a low calcium diet (under 200 mg per day) [2] It is at this level that the renal excretory capacity for calcium, in normal kidneys, is exceeded and hypercalcemia develops A normal person on such a low calcium diet excretes approximately 50 mg of calcium per day in his urine According to Pearson, destruction of 1 gm of bone per day, which releases about 100 mg of calcium, probably represents the minimum rate of osteolysis that can be measured by studies of urinary calcium excretion in patients with destructive bone tumors

Causes of hypercalcemia and hypercalciuria, other than bone tumors, such as hyperparathyroidism, osteomalacia, and osteoporosis, are usually differentiated by the clinical picture, the laboratory data, and the skeletal radiographs

Numerous investigators have shown that in every case of prostatic carcinoma with metastasis to bone, microscopically the lesions show evidence of both bone destruction and bone repair [3] According to Hellner,[4] and Axhausen,[5] every bone tumor, either primary or metastatic, begins with osteolysis Von Recklinghausen[6] in 1871 demonstrated that in metastasized prostatic tumors, bone formation

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Accepted for publication June 3 1957

[1] Griboff, S I Herrmann J B Smelin A and Mass, J Hypercalcemia secondary to bone metastases from carcinoma of the breast I *Relationship of serum calcium and alkaline* phosphatase values J Clin Endoc and Metab 14 379, 1954

[2] Pearson O H , West C D Hollander V P and Treves, W F Evaluation of endocrine therapy for advanced breast cancer J A.M A , 164 234, 1954

[3] Coley, B Neoplasms of Bone New York P B Hoeber, 1949, p 380–384

[4] Quoted by Coley, p 382

[5] Ibid

[6] Von Recklinghausen, F Die fibroese oder deformirende Osteitis, die Osteomalacie

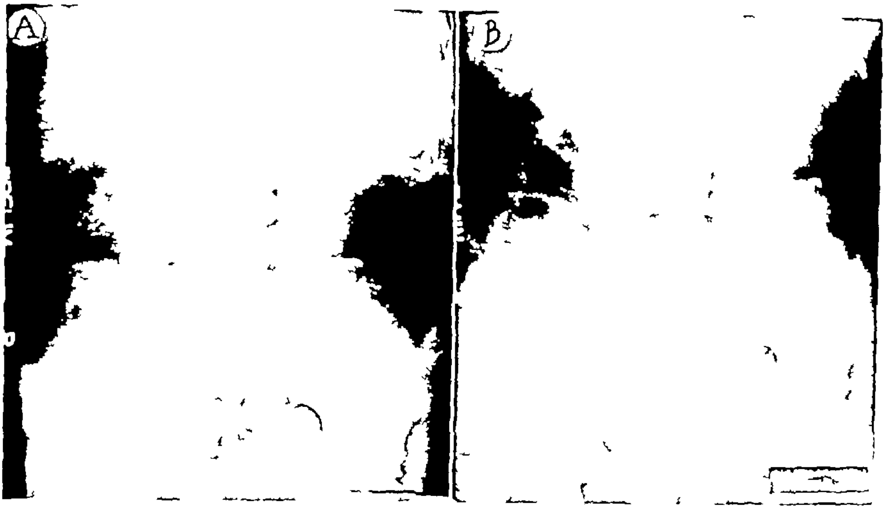

FIG 1 Typical example of extent of osteoblastic metastasis in cases discussed

usually predominates over bone destruction What we see therefore, in a roentgenogram of bone in metastasized prostatic carcinoma, is the predominating osteoblastic or osteolytic process

A study of 10 patients with biopsy-proven carcinoma of the prostate and marked osteoblastic bone metastasis was made to determine whether serum calcium levels or urinary calcium excretion could be used as an index of tumor growth as it is in carcinoma of the breast with metastasis to bone Because of the rarity of osteolytic metastastic lesions, this study was restricted to osteoblastic metastasis (fig 1) In whatever stage of treatment these patients were found, serum calcium, serum phosphorus, alkaline and acid phosphatase, renal function tests, and twenty-four-hour urinary calcium excretion were determined The patients had all been on a low-calcium diet (under 200 mg per day) for three days before these determinations were made All had normal renal function, evidenced in normal blood urea and creatinine, and phenolsulfonphthalein excretion Since none of the patients studied had any gastrointestinal lesions interfering with calcium absorption, fecal calcium excretion was not measured Concurrent bone destruction and formation were assumed, in accordance with the evidence of Hellner, Axhausen, Von Recklinghausen, and others Whether we could relate the urinary calcium excretion or serum calcium levels to metastasis to bone in these pateints was of interest

In table 1 the results of the chemical determinations are reported

In no case was the calcium loss sufficient to be reflected by abnormal increases in the urinary calcium excretion or in increased serum calcium levels In all but case 5, when calcium intake was restricted, urinary calcium excretion was in the range expected in normal persons Since excessive calcium deposition must have taken place before osteoblastic metastasis is visible in x-rays, one might expect

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und die osteoplastiche Carcinose in ihren gegenseitigen Beziehungen in Festschr Rudolph Virchow zu Seinem 71 Geburtstage Gewidmet von den Fruheren und Jetzigen Assistenten des Berliner Pathologischen Instituts Berlin G Reimer 1891, pp 1–89

TABLE I

Case	Age	℞	Serum Calcium	Serum Phosphorus	24-hour Urine		Alkaline Phosphatase Bodansky Units	Acid Phosphatase K A Units
					Ca	Ph		
			mg per cent	*mg per cent*	*mg*	*mg*		
1	75	None	8 8	3 4	60 91	790 412	not done	43 5
2	67	None	(every 2 wks) 9 0 8 7 8 5	2 7 2 9 4 0	38 56 50	640 410 760	12 0 15 5 9 0	41 2 21 0 18 0
3	71	None	(every 2 wks) 9 5 10 6 8 4	3 9 3 2 4 9	92 74 24	not done	2 0 1 2	4 4 2 0
4	71	Estrogens	9 7 10 2	2 6 4 0	70 102	690 295	24 5 18 0	30 4 24 5
5	65	Estrogens, orchiectomy	(every 2 wks) 8 4 8 6 7 4	3 0 3 1 3 2	81 64 trace	718 417 910	21 0 5 0 8 5	62 5 14 5 19 0
6	69	Estrogens orchiectomy	10 1 9 2	3 6 2 5	18 88	320 212	2 8 5 5	10 4 14 6
7	70	Estrogens, orchiectomy	9 0 8 4	2 7 2 7	41 32 71	not done 640 not done	not done	12 5
8	76	Before ℞ 8 weeks after orchiectomy estrogens	10 1 9 6	4 6	108 80	288 402	10 1 not done	190 0 not done
9	54	Orchiectomy estrogens	not done	not done	59	212	not done	not done
10	81	Estrogens orchiectomy	not done 9 1	3 3	79 69	818 495	22 0	87 0

a lower than normal urinary calcium excretion and perhaps lower serum calcium levels than we found The possibility that the calcium needs of the osteoblastic process were balanced by calcium loss from osteolysis was considered If osteolysis were not supplying calcium to the osteoblastic needs, we would expect a much lower urinary calcium output in these patients If an osteolytic process were masking an osteoblastic one, one would expect that when dietary calcium was restricted, urinary calcium excretion might be similar to that in the normal person on such calcium intake or in the calcium range found on our patients

Hypothetically, in these patients, if osteolysis were not supplying calcium one would expect excessively low urinary calcium excretion and possibly hypocalcemia We might assume then that calcium was made available to the osteoblastic components of these tumors by a significant, though roentgenologically not visible, osteolysis

Another factor makes the above conclusions less certain There is good evidence that the rate of growth of the metastatic lesions from prostatic carcinoma is slower than those of breast carcinoma According to Coley, progress is slower and survival is longer in osteoblastic forms of metastatic bone tumors This opinion is also held by Wolff who considered that osteoblastic predominance in a lesion indicates slower growth[7] Statistics on rates of growth of osseous metastatic lesions from breast and prostatic carcinoma are subject to many variables and are inherently difficult to compare In one series of 263 cases with osseous metastasis of prostatic carcinoma, close to 20 per cent of the patients lived five years after castration and endocrine therapy[8] In another series the average time from the development of osseous metastasis in patients who had undergone radical mastectomy and x-ray therapy to death was eighteen months,[9] while in still another series no patients with bone metastasis from breast carcinoma regardless of therapy were alive five years after the first evidence of bone metastasis[10] This strikingly demonstrates the slower rate of growth of osseous lesions in metastasized prostatic carcinoma The prognosis is better in metastasized prostatic tumors than breast tumors, even though the patients are older

Slow extension of osteoblastic prostatic metastasis requiring undetectable quantities of calcium, not reflected in abnormal urinary calcium excretion, might explain the normal range of urinary calcium excretion we found in these patients, without postulating the presence of significant concomitant osteolysis

SUMMARY

While osteolysis is proceeding in every case of osteoblastic metastasis from carcinoma of the prostate and there is some evidence that this may be of considerable magnitude, it is possible that the slow growth of osteoblastic metastatic lesions, rather than osteolysis, explains the pattern of urinary calcium excretion found in these patients

Urinary calcium excretion and serum calcium levels in these patients did not vary significantly from those in the normal person, and cannot be used to reflect the progress of osteoblastic metastasis from carcinoma of the prostate

The author wishes to thank Drs Henry M Weyrauch and Milton L Rosenberg for their assistance in preparing this paper

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CONGENITAL DEFICIENCY OF THE ABDOMINAL MUSCULATURE AND ASSOCIATED GENITOURINARY ANOMALIES A REPORT OF 22 CASES

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On the pediatric urological service of the Squier Clinic, 22 children have been seen who had congenital deficiency of the abdominal musculature, with or without associated genitourinary anomalies, since 1940 Before 1947 we had recognized only one patient with this syndrome, but since our interest and that of our colleagues on the pediatric service was heightened by the reporting of nine of our cases by Drs Eagle and Barrett in 1950, we have seen from one to three new cases each year since that time Twenty of the 22 children were males, and four of the 22 were Negroes These children were usually brought in during the first few days of life because of a large, flaccid abdomen through which the viscera could be palpated easily and through which the peristaltic movements of the intestines were clearly visible The seriousness of the large size of the abdomen was suggested by the fact that two of the children had sustained brain or spinal cord injuries during efforts to extract them at the time of delivery

Because of the lack of musculature in the abdominal wall the rib cages of these children did not retain the usual cylindrical shape and the costal margins usually flared out widely over the large abdomen The diaphragm was usually flattened out as a result This embarrassed respiratory function sufficiently that the children were very vulnerable to pneumonia Eighty five per cent showed some evidence of obstruction to the bladder outlet, with severe dilatation of the bladder, ureters and kidneys The testes had failed to descend in 18 (90 per cent) of the 20 male patients The testes were commonly found attached to the midureter, where a midline incision was required to reach them whenever orchiopexy was undertaken Anomalies of the lower extremity were present in nine (41 per cent), of whom six had bilateral clubfoot, one had unilateral clubfoot, one had a severely shriveled leg and the other had an absence of the lower leg on one side Eleven (50 per cent) of the patients had died before the age of 19 months and seven of these 11 had died within 12 days of birth because of severe kidney deficiencies or the replacement of the kidneys by a few cysts, with hypoplasia of the kidneys The others died of pneumonia or kidney abcesses

Other associated anomalies were frequent For instance, 28 per cent had anomalies of the intestines, ranging from two cases of abnormally loose mesentery of the cecum, to one megacolon, one imperforate anus, one anus emptying into the bladder, one atresia of the duodenum and one cystic fibrosis of the pancreas Other gastrointestinal anomalies may have been present but were not detected because the patients did well or because no autopsy was obtained (one

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Read at annual meeting of the American Association of Genito Urinary Surgeons, Hot Springs, Va , May 1-3 1957

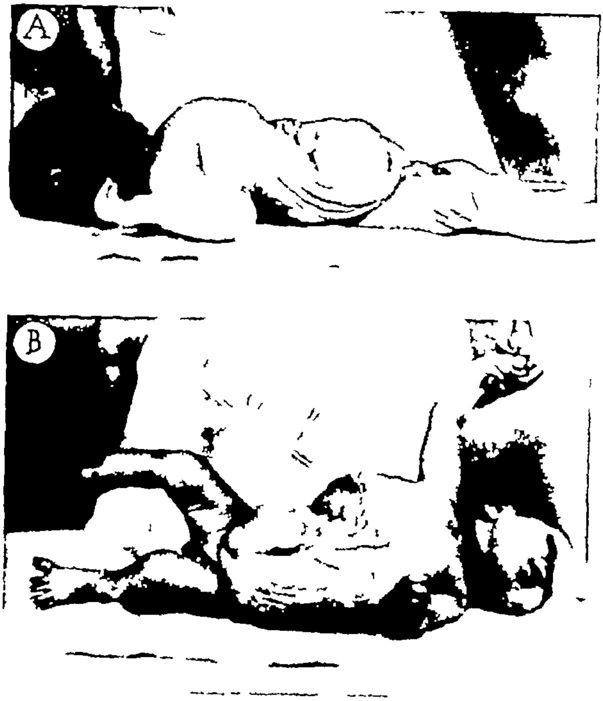

FIG 1 Newborn child, with complete absence of abdominal musculature both above and below umbilicus, who died at eight days after birth from uremia due to destruction of genitourinary tract Testes were not descended and costal margins flared out markedly Urachus was patent and drained urine soon after umbilical cord was cut

case) Cardiac anomalies were detected in five who came to autopsy and there were marked heart murmurs in two others, as well as electrocardiographic changes in a third, for a total of eight of the 22 patients Extra fingers or web toes were noted in two other patients Some of the findings in these 22 cases are tabulated in table 1

PATENT URACHUS

The urachus was patent and draining urine onto the abdominal wall in exactly 50 per cent (11) of our patients In most of these it appeared to represent the fact that the obstruction of the urinary tract was so severe that the allantoic remnant failed to close off, and extended up into the umbilical cord When the cord was cut at birth, this tract then became open to the outside and began to leak urine Of the 11 patients with a draining urachus, nine were dead within the first nine months of life and seven of the nine had died within the first 12 days after birth They did not necessarily die because of the open urachus, but because of severe kidney damage, probably associated with the fact that the pressure in the urinary tract had been sufficiently severe to cause the urachus to stay open Of the two who had an open urachus and survived, one healed spontaneously and the other was closed surgically when the patient was two years old It appeared that the urachus might represent a safety valve for the ob-

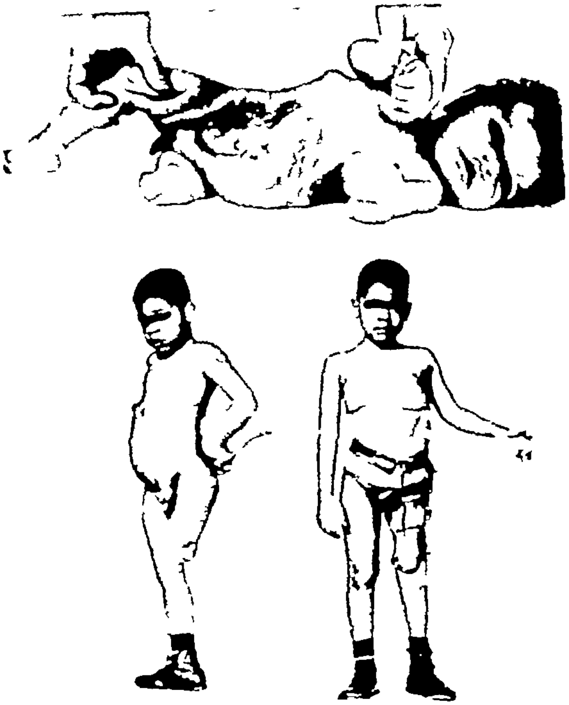

FIG 2 Photographs of same child at birth (above) and at age four years (below) showing that in spite of complete lack of abdominal musculature, patent urachus missing leg and undescended testes, growth and development have been satisfactory when urinary drainage was corrected and corset and other proper supports supplied

structed bladder if the kidney damage was not so severe as to fail to support life It is noteworthy that the incidences of these associated phenomena are similar to those reported in the literature for this syndrome The first nine patients in table 1 are those previously reported in 1950 by Eagle and Barrett, from this hospital The remaining cases have been discovered since that time One of the original nine cases was a boy (C E) of Dr Victor Marshall's from the New York Hospital, whose followup information he has graciously provided for us This child is doing well following bilateral operations to shorten and reimplant the ureters

PROGNOSIS

Both in this series and in the accumulated literature, approximately half the patients died within the first two years of life, usually because of severe damage to the kidneys from the urinary obstruction or, less often, from other causes such as cardiac anomalies or pneumonia due to the embarrassed respiratory apparatus Scattered cases in the literature have been reported as living to age 50 or 70 but no information was available as to whether or not genitourinary anomalies were present in these patients Of our own series, the two oldest children are now 13 years old and doing well If the urinary tract can be pro-

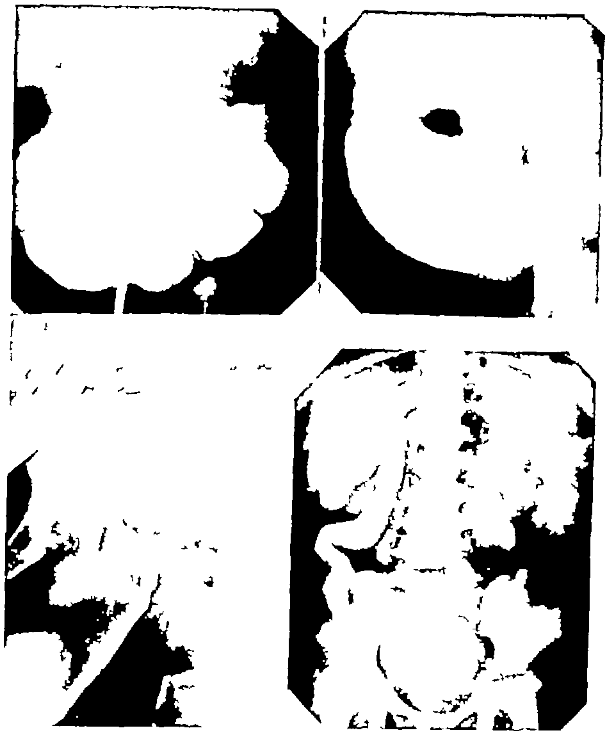

FIG 3 Shows dilated urinary tract at birth (upper left) and at age four years (lower right) Dilated urinary bladder is seen lying against inner surface of lower abdominal wall in photograph in upper right corner Elongated, narrowed urethra can be seen in urethrogram in photograph at lower left This patient had patent urachus closed, bladder neck obstruction resected and dilated and is now voiding normally and walking well with corset and artificial leg

vided with free drainage, if the kidney damage is not too extensive and if support can be provided for the flaccid abdomen there is no reason why these patients might not have a life expectancy in proportion to the amount of functioning kidney tissue still present when the condition is discovered Transurethral or open resection of the bladder outlet usually sufficed, but permanent diversion of the urine was necessary in a few cases Most of these children are still young and their final urinary status is not yet settled

PATHOGENESIS

Several intriguing theories have been advanced as to the relationship of the dilated urinary tract and the deficiency of the abdominal musculature The frequency of the association of the two conditions is so great as to suggest a cause and effect relationship However, our observations on this group of patients have led us to believe that there is no direct cause and effect relationship between the dilated urinary tract and the deficiency of the abdominal muscles We realize that the two conditions do usually occur simultaneously but feel that they are not necessarily dependent on each other for their causation

The most popular thesis which has been advanced suggests that the bladder dilates due to obstruction at the bladder neck and that the distended bladder causes pressure against the muscles of the abdominal wall, interfering with their development and resulting in atrophy or hypoplasia of the musculature in this area This possibility is supported by the fact that the most frequent muscle deficiency has been reported to exist in the region of the lower rectus muscles, where pressure from a distended bladder would come to bear Furthermore, it has also been observed that the next most common areas of abdominal muscular deficiency are those adjacent to the bladder area, whereas the musculature of the abdominal wall at the points most distant from the bladder, namely, in the flanks and the subcostal areas, shows no deficiency of abdominal musculature It has been suggested that the dilated ureters and bladder block the testes from descending Nevertheless, it appears to us that the following arguments represent a strong case against the theory that the pressure of the distended bladder *causes* faulty development of the abdominal musculature

Argument No 1 Two of our patients, Nos 10 and 19 on table 1 had normal urinary tracts with no distention of the bladder, yet had marked deficiencies of the abdominal musculature One was a male and one was a female Neither patient had obstruction of the bladder neck and the male did not have undescended testes, both testes were in the scrotum The muscular deficiency in these two patients certainly did not result from the pressure of a dilated bladder

Argument No 2 Many other patients exist who have very large urinary bladders as a result of obstruction, yet there is no deficiency of the abdominal musculature If the pressure of a distended bladder is likely to cause a failure of development of the abdominal musculature, the muscular deficiency should be a very common finding, rather than a very rare finding It has been suggested that perhaps some cases of obstruction occur at a later date or at a later stage of development in the embryo, after the abdominal muscles have formed, so that these patients show no muscle defects This appears to us to be unlikely

Argument No 3 Deficiency of abdominal musculature has often been ob-

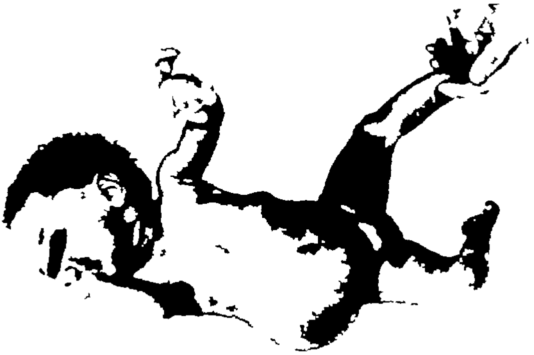

FIG 4 Muscular defect was primarily on right side Patient had bladder neck obstruction dilated urinary tract undescended testes and withered right foot

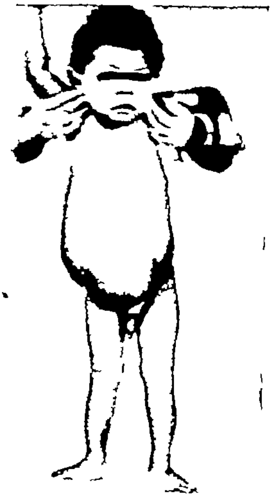

Fig 5

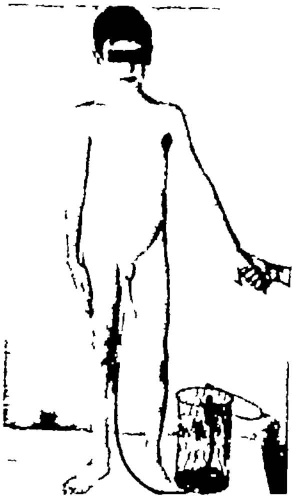

Fig 6

Fig 5 Another child where deficiency of abdominal musculature was primarily unilateral, on right side This child also had a dilated urinary tract, undescended testes and a heart murmur His growth and development have been good, after therapy

Fig 6 Child had no urinary symptoms noted until age of nine when he was found to have greatly dilated urinary tract due to fact that urine was mildly infected Child has refused operation but has tolerated inlying urethral catheter well and has shown some recovery of kidney architecture after prolonged catheter drainage

served in areas of the abdominal wall which could not possibly be pressed upon by a dilated urinary bladder, for instance, in areas above the umbilicus and in the flanks, where the bladder does not extend at any time, even when distended

Argument No 4 Unilateral distribution of areas of deficiency of the abdominal musculature is sometimes observed, as in cases 1 and 2 (figs 4 and 5) Here the deficiency was most marked in the upper right quadrants of the abdomen, far removed from any possible pressure by a dilated urinary bladder Another one of our cases showed a marked muscular deficiency in the left upper quadrant

Argument No 5 Histological studies of the abdominal musculature remnants which have been found in the abdominal walls of these children are reported to be much more suggestive of hypoplasia than of atrophy of differentiated muscle

There also appear to us to be arguments against the other main theory, namely, that the muscle deficiency in the abdominal wall is the primary lesion, and that the dilated urinary tract results because the abdominal muscles are necessary as accessory muscles of micturition, that the urinary tract empties poorly and therefore dilates when the muscles are deficient The arguments against this theory are as follows

Argument No 1 Two of our patients, Nos 10 and 19, had flaccid abdominal walls yet their urinary tracts did not dilate as a result This particular argument is weakened somewhat by the fact that both of these patients had some trace of rectus muscle or of rectus fascia over the bladder area even though there was obvious severe deficiency of the other muscles of the abdomen and a partial deficiency of the recti

Argument No. 2. A bladder outlet obstruction was demonstrated in 85 per cent of these patients. This is a strong argument that the urinary tract dilatation is due to obstruction of the bladder outlet rather than to the lack of abdominal musculature. Moreover, the walls of the bladder were usually thickened and trabeculated.

Argument No. 3. Patients with omphaloceles have no anterior abdominal musculature, yet do not commonly have dilatation of the urinary tract.

In spite of these strong arguments we feel that this theory bears more investigation. A suggestion that this condition is due to intrauterine poliomyelitis was refuted by the finding of a normal spinal cord in several of our patients, and in some cases in the literature that came to autopsy.

SUMMARY

When a deficiency of the abdominal musculature is found dilatation of the urinary tract will usually be found. However, we believe that the defect of abdominal musculature and the dilated urinary tract are not cause and effect but instead are associated anomalies. The dilated urinary tract appears to us to be usually due to bladder outlet obstruction frequently in the form of a membrane across the urethra at the level of the verumontanum of the type called "true valves of the urethra." The close association of these two anomalies may be due to a fault in the same organizer of the embryo, at some early stage, or to an insult occurring partway in the development of the embryo. It can not be argued that these two anomalies occur in otherwise normal children, as witness the fact that 40 per cent had anomalies of the legs, 28 per cent had anomalies of the gut and several had anomalies of the heart, pulmonary blood vessels and fingers. It is not even possible to say that these anomalies are limited to the lower half of the body.

Therapy must be directed to the relief of any bladder outlet obstruction and to the relief of other points of obstruction which may have developed due to the fact that the ureters have become tortuous and that the convolutions have become bound together by adhesions, causing kinks and additional points of obstruction. These may require nephrostomy first and straightening of the ureters later. Corsets or other therapeutic measures must be used to support the abdomen. In this way intestinal function will be improved, posture will be improved, and respiratory function will be improved when the dome of the diaphragm can be restored by maintaining intra-abdominal pressure.

From the clinician's standpoint it is essential that it be recognized that when a child has a flaccid abdomen he is likely to have severe dilatation of the urinary tract. Among our patients it appeared that if the condition was not recognized and treated, the chances were ten to one that the child would die an early death from uremia.

The author wishes to express his indebtedness to Drs. Dorothy Anderson, John K. Herd, Rustin McIntosh, J. Frederick Eagle, George S. Barrett, Aurelio Uson and the other members of the Medical Center staff who helped in the accumulation of this report.

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A URINARY ILEOSTOMY DEVICE

JACK LAPIDES, ROBERT BOYD AND SHELDON L. FELLMAN

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The use of an isolated loop of ileum as a common extension of the ureters through the abdominal wall was first popularized by Bricker in 1950.[1] Experience[2] with this method of supravesical diversion suggests that it is the best means of uretero-enterostomy at the present time. Because of lack of urinary stasis, absence of fecal stream and decreased intra-intestinal pressure, pyelonephritis has been decreased markedly. The ileal loop has been used at the University of Michigan Medical Center since 1952 in a variety of cases including paraplegia, myelomeningocele and spina bifida in children, bladder neoplasia, vesicovaginal fistulas, deteriorating ureterosigmoid transplants, etc.

Initially, we employed the usual types of fecal colostomy devices for collecting the urine, but soon became disenchanted with the various appliances because of bulkiness, leaking of urine, skin reaction, malodorousness and difficulty in changing the apparatus. Over the years with advice from our patients as well as our colleagues, we have evolved a device which appears to be efficient and reliable. The device consists of a small light-weight rubber ring with belt, condom, plastic plug, polyvinyl tubing and plastic urinal bag. The rubber ring and condom are the important parts of the apparatus, the tubing and urinal bag can be of rubber or plastic and of any type.

Unlike other types of enterostomy rings or cups, our rubber ring is not cemented to the skin but serves as a supporting frame for the condom which is cemented to the epidermis. Figures 1 and 2 depict the relationship between condom and rubber ring. Observe how the open end of the condom is brought through the opening of the rubber ring and stretched over the ring surface. The elasticity of the condom and the grooved lateral surface of the enterostomy ring keep the condom securely in place. Appropriate cement is applied to the skin surrounding the ileostomy as well as to that portion of condom stretched taut over the skinside of the ring. The ring and condom are then apposed to the skin. An elastic belt attached to the sides of the ileostomy ring helps to keep the device in a fixed position. The closed end of the condom is then connected to a tube either by rubber bands according to the method of Bors[3] or by means of a plastic plug.

The hollow plastic plug connecting the condom to the drainage tubing acts as a washer in that the closed end of the condom is pushed into the drainage tubing with the plug. It is necessary then to puncture the condom so that urine will flow freely from the condom into the drainage tubing.

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[1] Bricker, E. M.: Bladder substitution after pelvic evisceration. S. Clin. North Amer., 30: 1511, 1950.

[2] Lapides, J.: Unpublished data.

[3] Bors, E.: Personal communication.

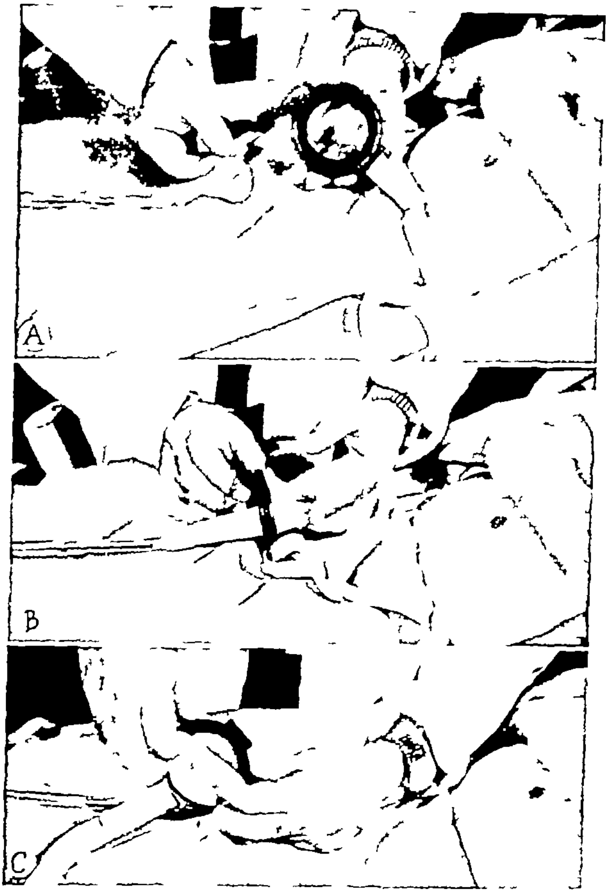

Fig 1

The advantages of this device are as follows

1) It can be applied to the patient at the operating table immediately upon completion of the ileostomy as well as being used as a permanent device postoperatively

2) The ring-condom-skin arrangement allows easy, rapid removal and replacement of the apparatus With a little solvent the skin is cleansed and the condom removed simultaneously The old condom is discarded and a new one put in its place No need to scrub the ring free of cement since its surface has never been in contact with the cement, for this reason, the rubber ileostomy ring will wear for a longer period of time

3) The use of a condom as part of the conduit system is advantageous because it stretches readily and thus acts as a safety valve If for some reason the tubing or urinal bag becomes occluded, urine can still be pumped by the ileum into the condom without appreciably increasing the intra-ileal or intra-ureteral pressures, and without forcing the device loose from the skin

4) The diameter of the hole in the ileostomy ring is so much larger than the

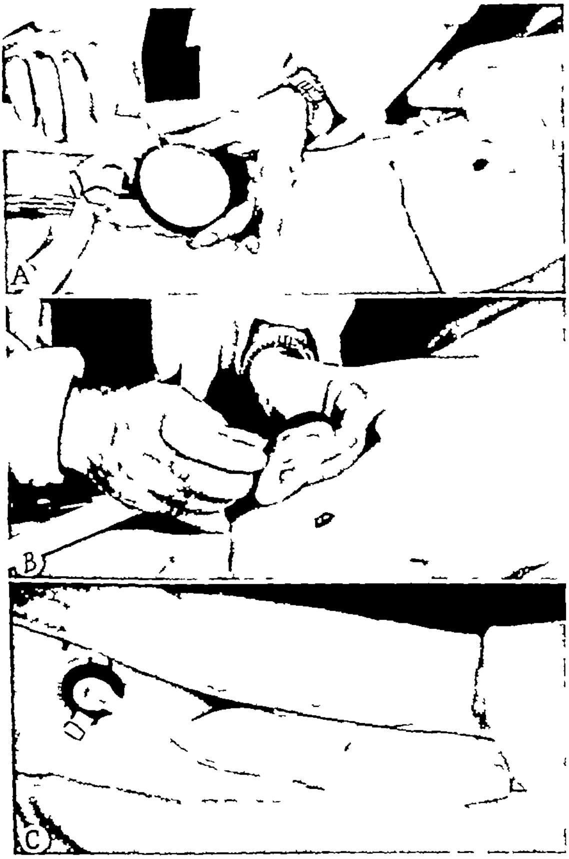

FIG 2

diameter of the ileostomy that it provides a nice wide margin of skin between the inner edge of the ring and the ileostomy This situation helps to prevent pressure necrosis of the ileum by an encroaching rim of ring, it also permits easier application of the ring to the skin because the patient does not have to be too exact in centering the ileostomy

5) It is neat and streamlined, permitting the patient to wear form-fitting clothes

The complete kit can be obtained from American Cystoscope Makers, Inc

We wish to express our appreciation to Mr Frederick J Wallace for his aid and advice in accomplishing this project

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CINEFLUOROGRAPHY FOR THE UROLOGIST

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Cinefluorography of the urinary tract is a practical clinical diagnostic tool in urology It is imperative, therefore, that the urologist not only understand the principles of this method and the use of the equipment, but also the radiation exposure factors This paper is therefore presented as an introduction to cinefluorography The historical background is also briefly presented

Photography is defined as the art or process of obtaining images on sensitized surfaces, by the action of light or other radiant energy Roentgenography is photography in which invisible or visible light is used, for example, roentgen radiation (invisible) and from the fluorescent screen (visible) Approximately one year following the discovery of the x-ray, Dr John Macintyre of Glasgow, Scotland, presented the first x-ray motion pictures (1896) This method consisted of x-raying a part on individual pieces of film by repositioning the part for each successive exposure The individual films are then rephotographed into conventional movie film and then projected In fact, the animated cartoons as produced today are done in this manner Dr Macintyre's motion picture consisted of individual radiographs of a frog's leg This was obtained by placing the motion picture camera behind a lead screen which contained an opening to match the opening of his camera The film was protected from visible light by a covering of black paper Manipulation of a frog and the camera and x-ray equipment was so difficult that Macintyre conceived the technique of photographing a part on individual pieces of film by repositioning the part for re-examination on successive exposures The resulting film, as previously stated, was then rephotographed to conventional motion picture film and projection In the same year (1896) Thomas Edison demonstrated his version of the motion picture camera in London, England Advances in motion picture work have progressed very rapidly to the present day cinemascope, television, etc Both Roentgen and Macintyre used a barium-platino-cyanide screen which under excitation by x-rays produced visible light Edison in 1896 discovered that calcium tungstate would fluoresce with an intensity six times greater than barium-platino-cyanide Patterson in 1914 introduced a cadmium sulfate screen, and this type of screen soon replaced those used by Roentgen and Macintyre In 1942, the Patterson Screen Company developed a zinc-cadmium sulfide screen which increased the brightness two and one-half times that of a type previously used Since that time further improvements have been made in what we know now as intensifying screens and fluoroscopic screens

Cineradiography consists of direct radiography of the moving part, utilizing the intensifying screens and the x-ray film apparatus and x-ray film Basically this is conventional radiography repeated at motion picture speeds and with full sized film Massive and expensive film apparatus and the large quantities of radiation required, of course, are undesirable under these circumstances

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Another method for producing x-ray motion pictures is called cinefluorography This consists of photographing a fluoroscopic screen with a motion picture camera This is also referred to as the indirect method Due to the small light collection factors for the motion picture camera lens and light losses in the lens, as well as a very low light intensity emitted from the screen, considerable radiation is required for satisfactory results In some cinefluorographic experiments, a radiation output of 100 milliamperes at 100 kilovolts has made it necessary to limit the total exposure time on the patient to 6 seconds

Dr Eugen Caldwell in the United States tried from 1908 to 1922 to do cinefluorography and cineradiography Keastler, Rider, and Rosenthal in 1909 made 13 successive x-rays in 22 seconds and placed this upon film as a motion picture showing the peristalsis in the stomach Cole in 1910, utilizing x-ray film 8 inches wide, exposed areas at regular intervals, then printed these on motion picture film Russell J Reynolds probably worked longer on this problem than any other man in medicine As recorded in literature, he began his work in 1921 and spent about 25 years utilizing variously improved fluorescent screens, camera and film to improve his technique The most early of investigators were limited to 5 and 6 second multiple exposures The literature is full of the many studies done by earliest investigators insofar as voltage, milliamperage, types of fluorescent screens, lenses of various focal length, color of fluorescence of the screen in relation to the film used, etc The limiting factor of the capacity of the x-ray tube and the tolerance of the patient's skin remained ever present

In order to obtain x-ray motion pictures, a number of factors have to be considered, A) the brillance of the screen image which is controlled by the fluorescent screen, B) the availability of film of extremely sensitive emulsions, C) the large aperture lens, D) the protection of the motion picture film from radiation, and E) the protection of the patient and medical personnel from excess radiation The recently developed devices for intensifying the brightness of fluoroscopic screens open up an entire new field of motion picture x-ray study This system of screen intensification utilizes an electronic tube principle To protect the patient from overexposure to radiation, the brillance required to produce a photographic effect must be obtained from some outside energy source by a tube amplification process rather than from increased x-ray intensity About 10 to 12 years ago devices to increase the intensity of fluoroscopic screens to a brilliance of several hundred times greater were described In the files of the U S Patent Office, sketches dated about 1915 showed a new electronic system of television which has since become the basis of present day television This was described as an attempt to increase the fluoroscopic screen brightness

Two types of screen intensifiers are currently in use One is that of the electronic tube system and the other, the television system Dr Russell Morgan and Mr Ralph Sturm of Johns Hopkins Hospital have developed a screen intensifier incorporating an image orthicon television chain, similar to that employed by television studios The major difference lies in its capability of scanning a picture frame with 1000 lines instead of the conventional 525 lines as is employed in commercial chains X-rays after passing through a patient are impinged upon a

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The second and most practical system of screen intensifications utilizes an electronic tube principle X-rays, after passing through the patient, impinge upon a fluorescent screen where the energy is converted to light This light ejects electrons from an adjacent photoelectric surface These electrons are focused by a system of electrostatic lenses mounted to an aluminum-backed phosphor layer All of the electrons from the input phosphor, which is a circular screen five inches in diameter, are concentrated on a circular phosphor layer one inch in diameter Simultaneously these electrons are accelerated so that they strike the output screen with increased velocity, which further increases the brilliance of the image Thus by concentration and acceleration of electrons, an image several hundred times brighter than the ordinary image is formed It must be emphasized that the vast increase in brightness is achieved without any increase in dosage of radiation to the patient It becomes entirely feasible and safe to obtain several minutes of cinefluorographic studies on a human subject since factors in the same order of magnitude as for ordinary fluoroscopy may be used For example, from 1 to 10 milliamperes and from 70 to 100 kilovolts can be utilized for satisfactory cinefluorography Furthermore, if the x-ray impulses are synchronized with a camera shutter, even less radiation is received by the patient For example, suppose a shutter speed of a movie camera is set at 15 frames per second, one cycle of the shutter operation therefore requires $\frac{1}{15}$ of a second Likewise, the film advances when the shutter is closed, requiring a $\frac{1}{30}$ of a second Since film is exposed during the period of advancement of the film, there is no reason to generate x-ray for this $\frac{1}{30}$ of a second per frame By generating x-rays only during the $\frac{1}{30}$ of a second that the shutter is open, four x-ray pulses are utilized for each frame Therefore, by synchronization, a total of 60 x-ray pulses per second are generated at the rate of four per frame to coincide with the time when the shutter is open This results in a 50 per cent reduction in radiation per second, or 50 per cent for the total cine-sequence

The urologist must know something about the exposure to radiation With the use of the present day image amplifiers, the usual exposure factors are from 1 to 5 milliamperes and 70 to 90 kilovolts Under these circumstances, somewhere in the vicinity of 3 to 3 5 roentgens per minute are liberated The skin erythema dose is somewhere in the vicinity of approximately 50 roentgens Therefore, the usual 50 per cent safety factor of 20 to 25 roentgens is the recommended maximum, and it is still further recommended that in most instances one should not exceed 10 to 15 roentgens Therefore, with an exposure factor of 3 to 3 5 roentgens per minute, 3 to 6 minutes of motion picture exposure may be safely obtained

It is imperative that one use either a time clock or a stop watch to measure the exact exposure of the patient to fluoroscopy This is important for both the patient and the operator

The field coverage of approximately 5 inches in diameter is a distinct disadvantage I am sure that future development will result in equipment of larger field coverage On viewing the cinefluorographic sequences as taken by the roentgenologist, we have frequently found that we failed to concentrate upon the areas of pathology or suspected pathology or have failed to place on film, in the proper position the sequence desired by us The urologist therefore need not only know and use properly the equipment, but he also must protect himself from radiation He must also think in terms of improving our cystoscopic tables, with lead shields to afford protection when doing retrograde pyelography in addition to cinefluorography We should like to emphasize again and again the importance that should be placed upon that of the urologist having knowledge of this particular type of equipment and the use of this equipment in order to gain maximum information from cinefluorography It is not our intention to minimize the role of the roentgenologist but to emphasize the fact that the urologist is better acquainted with the clinical findings in the particular patient involved and should be better able to interpret the areas of observation most important in the study of that patient

It has been stated that research will constitute approximately 40 per cent of cinefluorography use teaching an additional 40 per cent, and that patient service will be utilized in 20 per cent of the instances It is our personal feeling that cinefluorography will be the usual method of urography in the future and will constitute 100 per cent of use in the larger medical centers Instead of having four to six 14 inch by 17 inch pyelograms to review, five minutes of motion picture film taken at the rate of 15 frames per second will allow for review approximately 4 500 films which may be projected to any size desired Review of these films both in motion and in the still position, will give maximum information A projector that will allow a single frame and slow motion projection with simple stop and reverse and change to variable speeds is most helpful Such equipment, modified by Weinberg and Watson at the University of Rochester School of Medicine and utilized by Dr John Benjamin and associates at this same institution has been found to be most helpful in bringing to light normal and abnormal physiology not seen by the conventional type of intravenous or retrograde pyelographic studies For example review of the peristalsis of a ureter on a particular patient when seen through the ordinary projection of 15 frames per second revealed no unusual contraction wave of the intramural segment of the ureter In review of same sequence on the slow motion projector analyzer, three frames of film only showed a rapid elevation of the intramural segment of the ureter at the moment of emptying into the bladder Normal viewing of approximately 15 frames per second allows this sequence to be viewed in a period of one-fifth of one second This is obviously too fast to analyze by ordinary vision This example may be demonstrated and repeated over and over and over again The motion picture documentation of the movement of an organ in relation to time and examined by slow motion projection, superimposed over suitable graph paper in milliampere squares in the fixed projections, allows for an excellent study for ureteral and pelvic physiology In aortography and venography, slow speed visualization reveals the minor changes in the walls of blood vessels Needle biopsy of the kidney, using a Silverman needle under direct image amplification technique, has been done These studies, of course, are being done primarily in patients suffering from the nephritides, amyloidosis, nephrosis, and Kimmelstiel-Wilson disease, systemic lupus, etc

Future developments will, from an equipment standpoint, result in A) larger field coverage, B) a possible television type detector tube directly sensitive to roentgen rays, and/or C) increase the brightness still further of the phosphor layer to that of 5 to 25 times greater than that of the present screen Stereocinefluorography in which two roentgen ray tubes are used to expose film and then with a polarizing light film filtered on the two cameras and utilizing polaroid glasses giving third dimensional vision, has been used Placing of the x-ray tubes also in the anterior-posterior in addition to the side position with simultaneous exposure and recording has also been attempted for three-dimensional motion pictures Of course, there are still the hazards of radiation to be considered when one adds a second x-ray tube This is a serious problem at this time

The intravenous and retrograde routes of examination and manipulation have been utilized by us Retrograde procedures have of course necessitated the attempt to better protect ourselves from radiation We therefore are devising a lead shield to be used on a modified cinefluoro-cystoscopic table This will be described at a later communication Our findings have been varied and extremely instructive We wish merely here to summarize some of the interesting aspects of our findings which warrant further interpretation and study by varied investigators in the future

There are few studies of cinefluorography of the urinary tract in the literature Therefore, investigation must begin with normal physiology Narath described the levator muscles of the fornices and the sphincter of the fornices in addition to the longitudinal muscles of the calyces, which seem to consist of two portions, the upper part and the lower part He also described the sphincter of the calyces The collecting phase of urine into the calyces, pelvis, etc , is accompanied by relaxation of the levator muscles of the fornix and the sphincter of the fornix and the contraction of the upper part of the longitudinal muscles of the calyx, thus widening the upper portion of the calyx so that it appears somewhat as a goblet While this filling is complete, the empyting phase is accomplished by the relaxation of the sphincter and the contraction of the lower part of the longitudinal muscles of the calyx in addition to the contraction of the levator of the fornix and the sphincter of the fornix In this way the levator of the fornix holds the mucous membrane of the calyx on the papillae to prevent regurgitation of the urine into the papillary ducts In the meantime the ureteropelvic juncture is closed We were able to find changes in the calyces, infundibula, pelvis and ureter suggesting confirmation of Narath's studies Though there has been no definite sphincter demonstrated by histologic section in the area of the ureteropelvic juncture, it was obvious that the musculature in this area closes the pelvis during its filling from the calyces Thus urine cannot regurgitate into the pelvis from the ureter The area of closure of the ureter at the "ureteropelvic juncture" as we know of it, is actually below the juncture and the region of approximately the upper fourth of the upper third of the ureter This point has been repeatedly demonstrated on a number of occasions Review of a number of routine intravenous pyelograms will again demonstrate that there will be a filling of the pelvis and a small segment of the upper ureter beyond which there is no contrast material on a given film Although Narath and others have been unable to demonstrate the presence of sphincter muscles in segments of the ureter, cinepyelographic studies demonstrate that the ureter is divided into three anatomical divisions, each of which has a sphincter type of action preventing reflux of urine under usual circumstances As the pelvis contracts, the sphincters of the calyces contract to prevent regurgitation into the calyces The region below the ureteropelvic juncture opens to follow the propulsion of the urine down into the ureter The propulsion is rapid in the upper third of the ureter There is then a collection of contrast material with urine in the middle third of the ureter down to the region of the promontory There are frequently three to four contraction waves in the upper third as compared with one slow rolling type of contraction wave of the middle third of the ureter There seems to be a slow sludge through the ureter in the region of the promontory which is the widest portion of the ureter The lower third of the ureter has an extremely rapid type of contraction wave

Partial obstruction of the ureter at the ureteropelvic juncture (aberrant vessels, bands, or intrinsic ureteral obstruction with resultant hydronephrosis) will in some instances cause increased contraction of the renal pelvis with a slow emission of contrast material and urine into the ureter In other instances, the renal pelvis seems to have lost its forceful contractile ability and there are weak contraction waves In still other instances one may see a hydronephrotic pelvis with apparently normal jets of urine beyond the area of supposed obstruction This may possibly account for success and failure in ureteropelvic plastic repairs We are not at this time prepared to offer any definite conclusion in this regard The contraction waves of the calyces and pelvis vary from patient to patient In some patients there may be a contraction wave of all calyces simultaneously, whereas in other instances the contraction wave may be clockwise or counter clockwise in the respective calyces Some calyces seem to empty more completely than others, resulting in some instances in ‘residual urine in a calyx ”

More specific and extensive conclusions will warrant much more extensive studies by many investigators A plea, however, is again made for consideration ment of the ureter In review of same sequence on the slow motion projector analyzer, three frames of film only showed a rapid elevation of the intramural segment of the ureter at the moment of emptying into the bladder Normal viewing of approximately 15 frames per second allows this sequence to be viewed in a period of one-fifth of one second This is obviously too fast to analyze by ordinary vision This example may be demonstrated and repeated over and over and over again The motion picture documentation of the movement of an organ in relation to time and examined by slow motion projection, superimposed over suitable graph paper in milliampere squares in the fixed projections, allows for an excellent study for ureteral and pelvic physiology In aortography and venography, slow speed visualization reveals the minor changes in the walls of blood vessels Needle biopsy of the kidney, using a Silverman needle under direct image amplification technique, has been done These studies, of course, are being done primarily in patients suffering from the nephritides, amyloidosis, nephrosis, and Kimmelstiel-Wilson disease, systemic lupus, etc

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There are few studies of cinefluorography of the urinary tract in the literature Therefore, investigation must begin with normal physiology Narath described the levator muscles of the fornices and the sphincter of the fornices in addition to the longitudinal muscles of the calyces, which seem to consist of two portions, the upper part and the lower part He also described the sphincter of the calyces The collecting phase of urine into the calyces, pelvis, etc, is accompanied by relaxation of the levator muscles of the fornix and the sphincter of the fornix and the contraction of the upper part of the longitudinal muscles of the calyx, thus widening the upper portion of the calyx so that it appears somewhat as a goblet While this filling is complete, the empyting phase is accomplished by the relaxation of the sphincter and the contraction of the lower part of the longitudinal muscles of the calyx in addition to the contraction of the levator of the fornix and the sphincter of the fornix. In this way the levator of the fornix holds the mucous membrane of the calyx on the papillae to prevent regurgitation of the urine into the papillary ducts. In the meantime the ureteropelvic juncture is closed. We were able to find changes in the calyces, infundibula, pelvis and ureter suggesting confirmation of Narath's studies. Though there has been no definite sphincter demonstrated by histologic section in the area of the ureteropelvic juncture, it was obvious that the musculature in this area closes the pelvis during its filling from the calyces. Thus urine cannot regurgitate into the pelvis from the ureter. The area of closure of the ureter at the "ureteropelvic juncture" as we know of it, is actually below the juncture and the region of approximately the upper fourth of the upper third of the ureter. This point has been repeatedly demonstrated on a number of occasions. Review of a number of routine intravenous pyelograms will again demonstrate that there will be a filling of the pelvis and a small segment of the upper ureter beyond which there is no contrast material on a given film. Although Narath and others have been unable to demonstrate the presence of sphincter muscles in segments of the ureter, cinepyelographic studies demonstrate that the ureter is divided into three anatomical divisions, each of which has a sphincter type of action preventing reflux of urine under usual circumstances. As the pelvis contracts, the sphincters of the calyces contract to prevent regurgitation into the calyces. The region below the ureteropelvic juncture opens to follow the propulsion of the urine down into the ureter. The propulsion is rapid in the upper third of the ureter. There is then a collection of contrast material with urine in the middle third of the ureter down to the region of the promontory. There are frequently three to four contraction waves in the upper third as compared with one slow rolling type of contraction wave of the middle third of the ureter. There seems to be a slow sludge through the ureter in the region of the promontory which is the widest portion of the ureter. The lower third of the ureter has an extremely rapid type of contraction wave.

Partial obstruction of the ureter at the ureteropelvic juncture (aberrant vessels, bands, or intrinsic ureteral obstruction with resultant hydronephrosis) will in some instances cause increased contraction of the renal pelvis with a slow emission of contrast material and urine into the ureter. In other instances, the renal pelvis seems to have lost its forceful contractile ability and there are weak contraction waves. In still other instances one may see a hydronephrotic pelvis with apparently normal jets of urine beyond the area of supposed obstruction. This may possibly account for success and failure in ureteropelvic plastic repairs. We are not at this time prepared to offer any definite conclusion in this regard. The contraction waves of the calyces and pelvis vary from patient to patient. In some patients there may be a contraction wave of all calyces simultaneously, whereas in other instances the contraction wave may be clockwise or counter clockwise in the respective calyces. Some calyces seem to empty more completely than others, resulting in some instances in 'residual urine in a calyx.'"

More specific and extensive conclusions will warrant much more extensive studies by many investigators. A plea, however, is again made for consideration of the fair evaluation of the use of this type of equipment Cinepyelography seems to be the most efficient and practical manner of pyelographic study available to us today It is not unreasonable to predict image amplification in conjunction with closed circuit television for visual instrumentation of the urinary tract Our diagnostic and instrumental visualization of the urinary tract will be greatly enhanced by the application of image amplification

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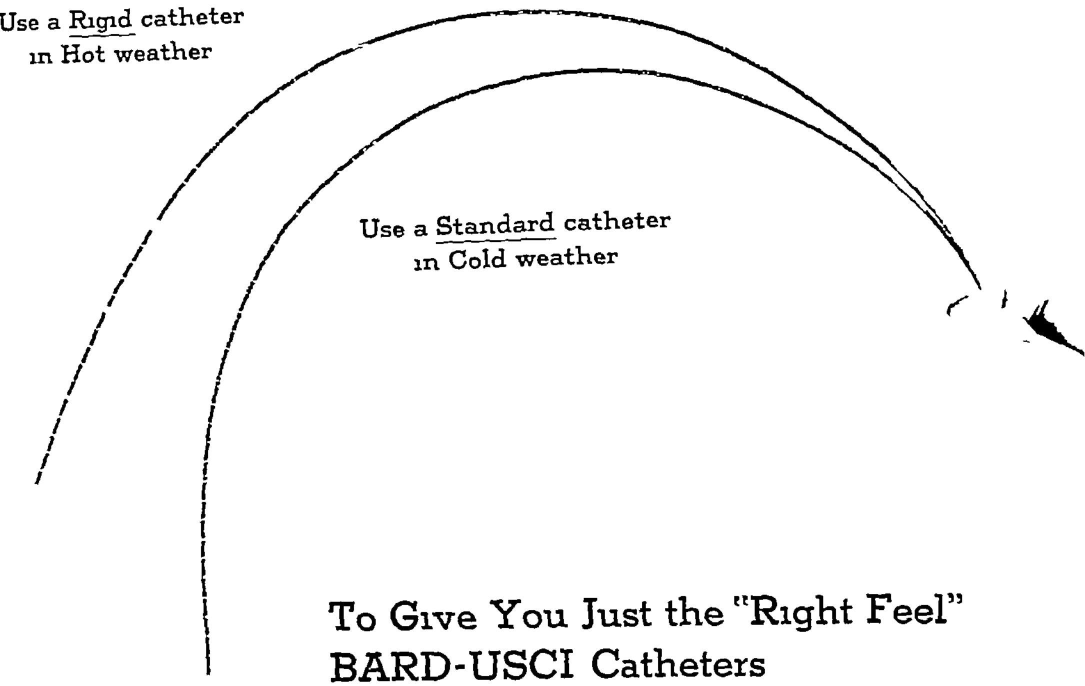

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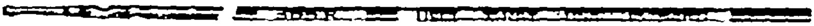
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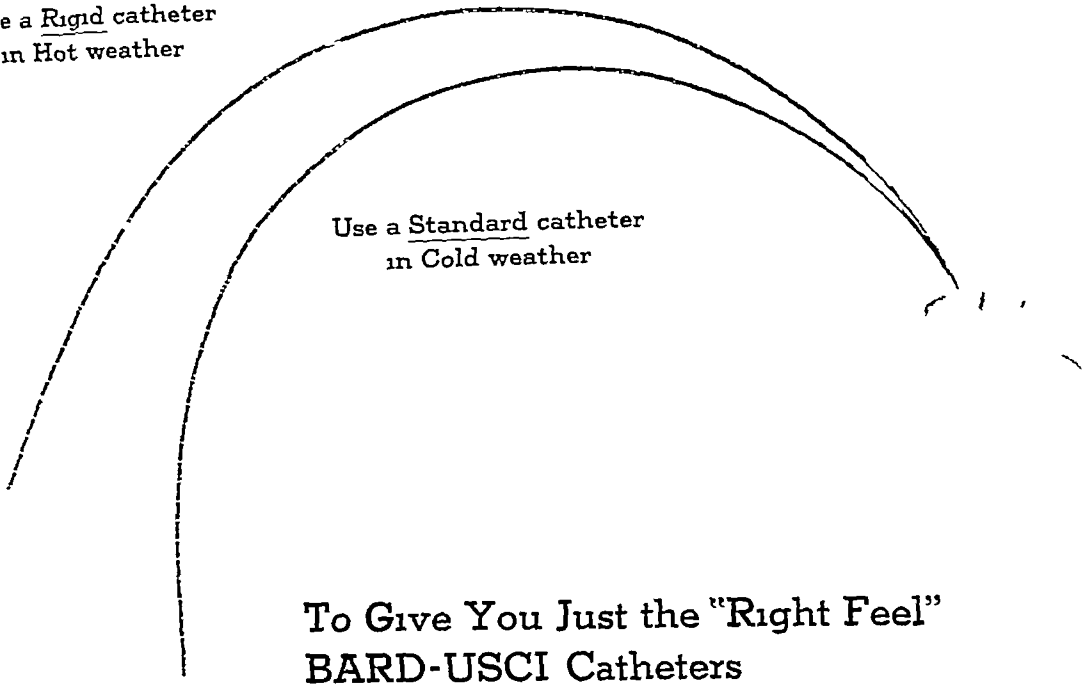

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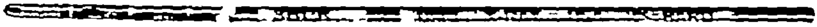

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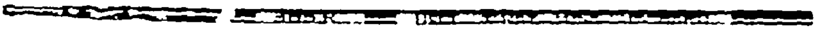

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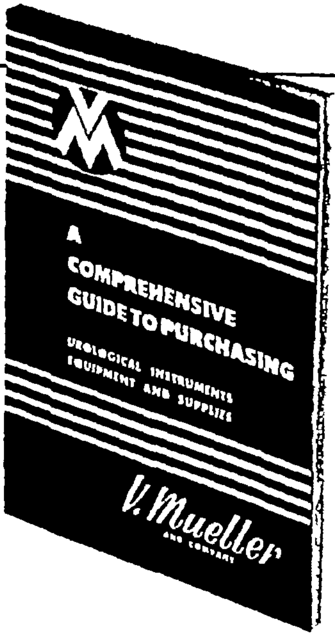

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